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Proposed Registration Decision PRD2014-19

Isofetamid

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Overview

Proposed Registration Decision for Isofetamid

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Technical Isofetamid Fungicide and Isofetamid 400SC Fungicide, containing the technical grade active ingredient isofetamid, to control various *Botrytis* and *Sclerotinia* diseases on grape, lettuce (head and leaf), rapeseed, low growing berry and turfgrass on golf courses and sod farms.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Technical Isofetamid Fungicide and Isofetamid 400SC Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on isofetamid, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on isofetamid, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Isofetamid?

Isofetamid is a broad-spectrum fungicide belonging to the SDHI (Succinate DeHydrogenase Inhibitors) group. It inhibits succinate-dehydrogenase in complex II of fungal respiration. Isofetamid is a locally systemic fungicide, which effectively controls fungal pathogens belonging to Ascomycetes (i.e. *Sclerotinia* spp.) and Deuteromycetes (i.e. *Botrytis* spp.). It has both preventative and curative properties.

Health Considerations

Can Approved Uses of Isofetamid Affect Human Health?

Isofetamid 400SC Fungicide, containing isofetamid, is unlikely to affect your health when used according to label directions.

Potential exposure to isofetamid may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the technical grade active ingredient isofetamid was of low acute toxicity by the oral, dermal and inhalation routes. It was non-irritating to skin, minimally irritating to eyes and did not cause an allergic skin reaction.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The acute toxicity of the end-use product Isofetamid 400SC Fungicide was low via the oral, dermal and inhalation routes of exposure. It was non-irritating to eyes and skin and did not cause an allergic skin reaction.

There was no evidence that isofetamid caused damage to the nervous system or immune system. There were no effects on the ability to reproduce. There was no evidence to suggest that isofetamid damaged genetic material and it did not produce tumours. Health effects in animals given repeated doses of isofetamid included effects on the liver, thyroid and body weight.

When isofetamid was given to pregnant rats, malformations in the cardiovascular system of the developing fetus were observed at a dose level sufficient to cause toxicity in the mothers.

The risk assessment protects against the effects of isofetamid by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and all infants (<1 year), the subpopulation which would ingest the most isofetamid relative to body weight, are expected to be exposed to less than 5% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from isofetamid is not of health concern for all population subgroups.

Isofetamid is not carcinogenic; therefore, a cancer dietary risk assessment is not required.

Acute dietary (food plus drinking water) intake estimate for female 13-49 years old was less than 5% of the acute reference dose and is not a health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and/or the United States using isofetamid on grape, lettuce, strawberry, canola and almond are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this Consultation Document.

Risks in Residential and Other Non-Occupational Environments

Risks in Non-Occupational Environments

Non-occupational risks are not of concern when Isofetamid 400SC Fungicide is used according to the proposed label directions.

Adults and youth may be exposed to isofetamid while golfing on treated courses. Based on the expected short to intermediate term duration of this activity, risk to golfers is not a concern.

Adults, youth and toddlers may be exposed to isofetamid during pick-your-own harvesting activities. Based on the expected acute term duration of these activities, risk to the general population is not of concern.

Occupational Risks From Handling Isofetamid 400SC Fungicide

Occupational risks are not of concern when Isofetamid 400SC Fungicide is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Isofetamid 400SC Fungicide as well as field workers entering treated fields can come in direct contact with isofetamid residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying Isofetamid 400SC Fungicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing/loading, application and during clean-up and repair. The label also requires that workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk from exposure to isofetamid for these individuals is not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Isofetamid Is Introduced Into the Environment?

Isofetamid is moderately persistent with the main route of dissipation in the terrestrial environment being biotransformation and uptake into plants. One major transformation product, 4-HP, and several minor transformation products of isofetamid were identified in soil studies. Isofetamid can enter the aquatic system through spray drift and runoff from treated fields. In aquatic systems, isofetamid transforms rapidly via phototransformation in shallow, clear waters to the major transformation products PPA and IBA. In deeper waters, isofetamid sorbs to sediment.

The risk to the environment was assessed for the isofetamid end-use product Isofetamid 400SC Fungicide. In the terrestrial environment, Isofetamid 400SC Fungicide at the proposed application rates and use pattern may pose a risk to birds and small wild mammals. No risk was identified to earthworms, bees, beneficial predatory and parasitoid insects or terrestrial plants.

In the aquatic environment, Isofetamid 400SC Fungicide, at the proposed application rate and use pattern, is expected to pose an acute risk to fish and aquatic invertebrates. Several groups of animals are at risk from chronic exposure to isofetamid, including fish, amphibians, and freshwater aquatic invertebrates. As isofetamid residues are moderately persistent in aerobic aquatic and in anaerobic aquatic sediments, prolonged exposure of aquatic organisms to isofetamid may occur under the proposed use pattern.

These risks may be mitigated by applying spray buffer zones and label statements. To reduce the potential risk from runoff, advisory statements are included on the label. Hazard statements will be required on the product label for birds and small wild mammals.

Isofetamid is not expected to bioconcentrate or bioaccumulate in aquatic organisms.

Value Considerations

What Is the Value of Isofetamid 400SC Fungicide?

Isofetamid 400SC Fungicide, containing isofetamid, has demonstrated effectiveness in controlling botrytis bunch rot on grape, sclerotinia drop on lettuce (head and leaf), sclerotinia stem rot on rapeseed (Crop Subgroup 20A), grey mold on low growing berry (Crop Subgroup 13-07G), and dollar spot on turfgrass on golf courses and sod farms. Isofetamid 400SC Fungicide is formulated in suspension concentrate (SC) and applied as a foliar treatment. Isofetamid 400SC Fungicide adds another mode of action which will contribute to the disease management options for these targeted diseases. In addition, Isofetamid 400SC Fungicide is reviewed under the NAFTA Priority Joint Review program with US EPA; therefore, registration of this product will bring the same technology to Canadian growers and their US counterparts.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Isofetamid 400SC Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with isofetamid on the skin or through inhalation of spray mists, anyone mixing, loading and applying Isofetamid 400SC Fungicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing/loading, application and during clean-up and repair. Entry into treated areas is restricted for 12 hours after application. Use in greenhouses, on residential lawns and by aerial application is restricted. In addition, standard label statements to protect against drift during application were added to the label.

Environment

Hazard statements for birds, small wild mammals and aquatic organisms will be added to the product label. Buffer zones to prevent spray drift to aquatic environments will also be added.

Next Steps

Before making a final registration decision on isofetamid, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

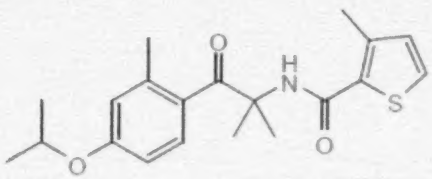
When the PMRA makes its registration decision, it will publish a Registration Decision on isofetamid (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Isofetamid

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Isofetamid
Function	Fungicide
Chemical name	
1. **International Union of Pure and Applied Chemistry (IUPAC)**	*N*-[1,1-dimethyl-2-(4-isopropoxy-*o*-tolyl)-2-oxoethyl]-3-methylthiophene-2-carboxamide
2. **Chemical Abstracts Service (CAS)**	*N*-[1,1-dimethyl-2-[2-methyl-4-(1-methylethoxy)phenyl]-2-oxoethyl]-3-methyl-2-thiophenecarboxamide
CAS number	875915-78-9
Molecular formula	$C_{20}H_{25}NO_3S$
Molecular weight	359.48
Structural formula	
Purity of the active ingredient	96.3%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Isofetamid Technical

Property	Result
Colour and physical state	Pale brown powder
Odour	Odourless
Melting range	103.5 – 105.0°C
Boiling point or range	Decomposes at >176°C without boiling
Relative density	1.18
Vapour pressure at 20°C	4.2×10^{-7} Pa
Henry's law constant at 20°C	1.2×10^{-5} Pa.m^3.mol^{-1}
Ultraviolet (UV)-visible spectrum	$\lambda_{max} \approx 260$ nm, no absorbance >340 nm in acidic, neutral and basic media

Solubility in water at 20°C	5.33 mg/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) n-heptane — 1.2 n-octanol — 31.7 xylene — 61.4 1,2-dichloroethane — >250 acetone — >250 methanol — >250 ethyl acetate — >250
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} 2.5
Dissociation constant (pK_a)	Does not dissociate between pH 4-10
Stability (temperature, metal)	Stable in contact with iron, aluminum, iron acetate or aluminum acetate at 54°C; photochemical degradation: half-life = 1.38 h

End-use Product— Isofetamid 400SC Fungicide

Property	Result
Colour	Off-white
Odour	Odourless
Physical state	Liquid
Formulation type	Suspension concentrate
Guarantee	400 g/L
Container material and description	Plastic bottle or drum, 500 mL to 200 L
Density	1.09 – 1.12 g/mL
pH of 1% dispersion in water	6-8
Oxidizing or reducing action	Not expected to be oxidizing based on composition
Storage stability	Product was stable in both HDPE and PET after 2 weeks storage at 54°C, after 7 days storage at 0°C, and after 2 years storage under warehouse conditions (temperature range from -3 to 29°C).
Corrosion characteristics	Not corrosive to HDPE or PET in accelerated or long-term storage stability studies
Explodability	Not expected to be explosive based on composition

1.3 Directions for Use

Isofetamid 400SC Fungicide is formulated as a foliar treatment against various *Botrytis* and *Sclerotinia* diseases on grape, lettuce (head and leaf), rapeseed (Crop Subgroup 20A), low growing berry (Crop Subgroup 13-07G), and turfgrass on golf courses and sod farm. The use rates ranged from 0.75 to 1.61 L/ha on the associated agricultural crops or from 12.7 to 15.9 mL/100 m^2 on turfgrass. Under conditions favorable for disease development, the higher rate specified and shorter application interval should be used. Preventive applications are recommended. Optimal disease control is achieved when Isofetamid 400SC Fungicide is applied as part of an integrated pest management (IPM) program.

1.4 Mode of Action

Isofetamid, a Group 7 fungicide (Carboxamides), inhibits succinate-dehydrogenase (SDH) in complex II of fungal respiration. The target enzyme of SDH inhibitors is succinate dehydrogenase, which is a functional part of the tricarboxylic cycle and linked to the mitochondrial electron transport chain. Isofetamid has both preventative and curative properties. Isofetamid is also known to have local systemic (or translaminar) transport against the various stages of fungal growth.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Table 1 in Appendix I.

2.4 Methods for Residue Analysis

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Method JSM0119 in plant matrices) were developed and proposed for data generation and enforcement purposes. The HPLC-MS/MS Method SMV 8256542-04V and SMV 8256542-03V were developed for data generation purposes in animal matrices. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant matrices. The proposed enforcement method for plant matrices was successfully validated by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled samples (grape, lettuce, almond and dry bean) analyzed with the enforcement method.

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Method SMV 8256542-03V and SMV 8256542-04V in animal matrices) were developed for data generation purposes. An enforcement method for edible livestock commodities is not necessary, given that MRLs are not being proposed due to negligible

potential for residue transfer to these matrices as a result of the proposed uses. However, in the event that MRLs are required for livestock commodities due to the potential of residue transfer from a new use pattern, an adequate enforcement method for livestock commodities will be required. Methods for residue analysis are summarized in Table 1, Appendix I.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for isofetamid was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to isofetamid.

Absorption and excretion were rapid in both sexes of rats given single high, low or repeat low oral doses of radiolabeled isofetamid. Bile duct cannulation revealed that absorption was high for both sexes. Maximum plasma concentrations were achieved between 2 and 6 hours at the low-dose and approximately 8 hours at the high dose. The majority of the administered dose (AD) was eliminated in the excreta within 48 hours, with elimination essentially completed by 4 days. Feces was the predominant route of excretion. Urinary excretion in females was approximately five times higher than in males. Excretion of radiolabel through bile was also high in the bile duct cannulated rats suggesting reabsorption of biliary metabolites followed by excretion through the urine. Radiolabel recovery from expired air was negligible. The half-life of elimination was approximately 38 hours regardless of sex, dose or radiolabel position. Residues in tissues 7 days post-administration were low with the highest levels found in the liver, GI tract and carcass of both sexes. The levels of radioactivity were evenly distributed across other organs and tissues. The most significant difference of high versus low dosing was an increase in urinary excretion of radiolabel in low dose females. There was no evidence of accumulation of radioactivity in tissues or organs.

Isofetamid underwent extensive metabolism following oral administration with no qualitative sex or radiolabel differences in metabolism. The test material was rapidly metabolized by O-dealkylation, hydroxylation, and subsequent glucuronidation. Minor routes included methylation, sulfation and cleavage between the benzene and thiophene-ring. Unmetabolized parent compound was identified in the feces.

The acute toxicity of isofetamid was low via the oral, dermal and inhalation routes in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits. Isofetamid was not a skin sensitizer in mice by the LLNA method.

The acute toxicity of the end use product Isofetamid 400SC Fungicide was low via the oral, dermal and inhalation routes in rats. It was non-irritating to the eyes and the skin of rabbits. It was not a skin sensitizer in mice by the LLNA method.

Short-term, repeat dose feeding studies in mice, rats and dogs with isofetamid revealed effects on the liver, thyroid and adrenals and on body weight. Compared to controls, mice treated with isofetamid had decreased body weight gain and increased adrenal weight with cortical hypertrophy, increased liver weight with hepatocellular hypertrophy and clinical chemistry alterations. Effects in rats treated with isofetamid included increased adrenal weight, increased liver weight with hepatocellular hypertrophy, increased thyroid follicular cell hypertrophy, increased prothrombin/thromboplastin time and clinical chemistry alterations. At higher dose levels, rats also had dark livers and increased adrenal hypertrophy. Treatment of dogs via capsule administration with isofetamid resulted in increased liver weights, hepatocellular hypertrophy, darkened and visibly enlarged livers as well as thyroid follicular cell hypertrophy, adrenal hypertrophy, decreased body weight gains and clinical chemistry alterations. A 28-day repeat dose dermal toxicity study in rats produced no systemic toxicity up to the limit dose.

Isofetamid was administered in the diet of mice and rats in long-term studies. In the mouse oral study, liver and adrenal weights were increased while body weights were decreased at the highest dose level. Administration of isofetamid to rats for one or two years resulted in increased liver and thyroid weight with concordant histopathological and clinical chemistry effects as well as tubular basophilic change in kidneys. There were no treatment-related tumours in either mice or rats following two years of treatment with isofetamid. There was no evidence of increased toxicity in any test species with increased duration of dosing.

There was no evidence of mutagenic or clastogenic potential of isofetamid observed in the genotoxicity battery of studies which included an Ames assay, an in vitro Chinese hamster lung cell clastogenicity assay, a mouse lymphoma gene mutation assay and an in vivo mouse micronucleus assay.

In a dietary multi-generation rat reproductive toxicity study, parental toxicity included increased liver and thyroid weights along with increased hepatocellular hypertrophy and thyroid follicular cell hypertrophy in both sexes and both generations. Also observed were increased liver cytoplasmic eosinophilic inclusion bodies and decreased spleen weight in F_1 males and increased body weight gain during lactation in both generations of females. The offspring of both generations exhibited decreased body weight and body weight gains, mostly during post-natal days 14-21, possibly reflecting direct compound consumption. Also observed were decreased absolute spleen and thymus weight in both sexes and both generations. The young animals did not demonstrate increased sensitivity to isofetamid in this study.

In a rat oral developmental toxicity study, there was a single fetus with several cardiovascular system malformations at the mid-dose. The possible association with treatment could not be ruled out in light of the fact that similar malformations were noted in two fetuses from separate litters at the next highest dose (the limit dose). When considering the study as a whole, the incidence of malformations in the three animals was above the historical control range. Salivation, chin rubbing and increased liver weight were observed in the mid-dose dams. Although the findings in dams were questionable in terms of demonstrating toxicity, histopathology and clinical chemistry assessments were not performed and the other short-term rat toxicity studies suggest that liver-related toxicity would likely have been observed at these

doses. The rabbit oral developmental toxicity study produced increased liver weight in doses at the limit dose and no adverse effects at any dose in the fetuses. There was no evidence of sensitivity of the young in rabbits.

Functional observational batteries for neurotoxicity in repeat dose dietary rat toxicity studies were negative. In the rat acute neurotoxicity study, decreased ambulatory motor activity in females was observed at the limit dose. There was no evidence of neurotoxicity in the rat 90-day repeat dose neurotoxicity study. The weight of evidence suggests isofetamid is not neurotoxic.

In a mouse dietary 28-day antibody plaque-forming cell assay with isofetamid, there was an increase in liver weight at the high dose. There was no evidence of immunotoxicity.

Results of the toxicology studies conducted on laboratory animals with the end-use product Isofetamid 400 SC Fungicide and technical active isofetamid are summarized in Tables 2 and 3, respectively, of Appendix I. Effects seen above the LOAEL(s) have not been reported in Table 3 for most studies for reasons of brevity. The toxicology endpoints for use in the human health risk assessment are summarized in Table 4 of Appendix I.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents from Canada and the United States were searched for isofetamid, and any additional information submitted by the applicant during the review process was considered. As of May 13, 2014, there were no health-related incident reports for isofetamid reported to the PMRA and the applicant did not submit any additional data.

3.1.1 Pest Control Products Act Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of required studies was available including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of the fetus compared to maternal animals in the rat developmental toxicity study. There were slightly increased incidences of cardiovascular system malformations in rat fetuses. These serious effects occurred at doses considered sufficient to produce some toxicity in the dams. There were no adverse effects observed in developing rabbits. The two-generation rat reproductive toxicity study did not identify any reproductive toxicity effects. Observations in the offspring of that study were limited to decreased spleen and thymus weight and decreased body weight and body weight gain, likely due to direct compound consumption during lactation. There was concordant toxicity in the parental animals at the same dose level.

Overall, the database is adequate for determining the sensitivity of the young. The fetal malformations in rats were considered serious endpoints, although the concern was tempered by the presence toxicity in adult rats at the same dose levels. The *Pest Control Products Act* factor was reduced to 3-fold for scenarios in which this endpoint was selected as the point of departure for risk assessment. For all other scenarios, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

Acute Reference Dose (females 13-49 years of age)

To estimate acute dietary risk (1 day), the rat developmental toxicity study with a NOAEL of 100 mg/kg bw/day for developmental toxicity was selected for risk assessment. At the LOAEL of 300 mg/kg bw/day, a fetus had multiple malformations of the cardiovascular system. Two fetuses from two litters had similar effects at 1000 mg/kg bw/day. These effects may result from a single exposure to isofetamid and are therefore relevant to the establishment of an ARfD. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 3-fold. **The composite assessment factor (CAF) is 300.**

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{100 \text{ mg/kg bw}}{300} = 0.3 \text{ mg/kg bw of isofetamid}$$

Acute Reference Dose (general population excluding females 13-49 years of age)

No acute endpoints of concern relevant to the general population were identified in the toxicology database so an ARfD was not established for this group.

3.3 Acceptable Daily Intake (ADI) for general population

To estimate risk from repeated dietary exposure, the 1-year dog toxicity study with a NOAEL of 5.3 mg/kg bw/day was selected for risk assessment. The LOAEL of 166 mg/kg bw/day was based on liver effects including increased weight, hypertrophy and clinical chemistry changes. This study provides the lowest NOAEL in the database and was considered the most appropriate for the risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The CAF is 100**.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5.3 \text{ mg/kg bw/day}}{100} = 0.05 \text{ mg/kg bw/day of isofetamid}$$

The ADI provides a margin of 2000 to the NOAEL for malformations in the rat developmental toxicity study.

Cancer Assessment

There was no treatment-related increase in tumours in rats or mice; therefore, a cancer risk assessment was not required.

3.4 Occupational and Residential Risk Assessment

Short- and Intermediate-term Dermal Exposure (Adults)

For short- and intermediate-term dermal risk assessment for adults, the oral developmental toxicity study in rats was selected. The 28-day dermal toxicity study in rats did not address the endpoint of concern, namely malformations, thus necessitating the use of an oral study for risk assessment. At a dose of 300 mg/kg bw/day, a single fetus exhibited multiple malformations in the cardiovascular system. There were two individual fetuses from separate litters at 1000 mg/kg bw/day with similar effects. Dose levels of 300 mg/kg bw/day were considered to be toxic to the dams. A NOAEL of 100 mg/kg bw/day was established for both maternal and developmental toxicity.

For occupational scenarios, the target MOE selected for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability and a three-fold factor was applied due to the concerns identified in the rat oral developmental toxicity study. This MOE is considered to be protective of all adults, including pregnant women and their unborn children. For residential scenarios, the *Pest Control Products Act* factor was reduced to 3-fold as outlined in the *Pest Control Products Act* Hazard Characterization section.

Short- and Intermediate-term Inhalation Exposure (Adults)

For short- and intermediate-term exposure via the inhalation route, the oral developmental toxicity study in rats was selected for risk assessment. A short-term inhalation study was not available and would not have addressed the endpoint of concern. A NOAEL of 100 mg/kg bw/day was established based on a single fetus with multiple malformations and toxicity in the maternal animals at 300 mg/kg bw/day.

For occupational scenarios, the target MOE selected for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability and a three-fold factor was applied due to the concerns identified in the rat oral developmental toxicity study. This MOE is considered to be protective of all adults, including pregnant women and their unborn children. For residential scenarios, the *Pest Control Products Act* factor was reduced to 3-fold as outlined in the *Pest Control Products Act* Hazard Characterization section.

Short- and Intermediate-term Dermal Exposure (Youths)

For short- and intermediate-term residential dermal risk assessment for children, the short-term dermal toxicity study in rats was selected. A NOAEL of 1000 mg/kg bw/day was established as there were no adverse effects observed.

For residential scenarios, the target MOE selected for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. This MOE is considered to be protective of children.

Short- and Intermediate-term Inhalation Exposure (Youths)

For short- and intermediate-term residential inhalation risk assessment for children, the short-term (90-day) oral toxicity study in rats was selected. A NOAEL of 7 mg/kg bw/day was established based on liver toxicity and clinical chemistry alterations at the LOAEL of 70 mg/kg bw/day.

For residential scenarios, the target MOE selected for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. This MOE is considered to be protective of children.

Aggregation of Short- and Intermediate-term Oral and Inhalation Exposure (Youths)

For aggregation of short- and intermediate-term residential oral and inhalation risk assessments for children, the short-term (90-day) oral toxicity study in rats was selected. A NOAEL of 7 mg/kg bw/day was established based on liver toxicity and clinical chemistry alterations at the LOAEL of 70 mg/kg bw/day. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. This MOE is considered to be protective of children. A dermal component was not required for this aggregation as a common endpoint (liver toxicity) was not observed in the rat short-term dermal study.

Aggregation of Short- and Intermediate-term Oral, Dermal and Inhalation Exposure (Adults)

For an aggregation of short- and intermediate-term residential exposure via the oral, inhalation and dermal routes, the oral developmental toxicity study in rats was selected. A NOAEL of 100 mg/kg bw/day was established based on a single fetus with multiple malformations and toxicity in the maternal animals at 300 mg/kg bw/day. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. The *Pest Control Products Act* factor was reduced to 3-fold as outlined in the *Pest Control Products Act* Hazard Characterization section.

3.4.1 Toxicological Endpoints

Occupational exposure to isofetamid is characterized as short- to intermediate- term and is predominantly by the dermal and inhalation routes. Non-occupational exposure to isofetamid is characterized as acute, short- or intermediate-term and is predominantly by the dermal and oral routes.

3.4.1.1 Dermal Absorption

Four dermal absorption studies were submitted by the applicant for determination of dermal penetration of isofetamid during occupational exposure: a rat *in vivo* study (high, intermediate, low doses); a rat *in vitro* study (high, intermediate, low doses); a human *in vitro* study (high, intermediate doses); and a second human *in vitro* study (high, low doses). According to PMRA guidance, a human *in vitro* dermal absorption study may be included as part of a triple pack approach with animal *in vivo* and *in vitro* studies provided that certain minimum standards and criteria are met such as standard study guidelines are followed, no major limitations are evident, a sufficient number of replicates are performed and the ratio between percent absorption in the animal *in vivo* and *in vitro* studies is close to one. Following the review of the studies it was noted that the ratio between the submitted rat *in vivo* study and *in vitro* studies was not close to one. As such, the *in vitro* studies were not accepted and the rat *in vivo* study alone was used to predict dermal absorption.

The dermal absorption of 13% for isofetamid from the *in vivo* rat dermal absorption study was considered most appropriate for risk assessment purposes. Review of the study indicated that it is

acceptable and no major limitations were evident. Four rats per dose group were sampled over three doses. The high dose was equivalent to the commercial formulation of the product and the intermediate and low doses were intended to represent the in-use application rates of the product. The dermal absorption value was based on the combined residues found in the excreta (urine, faeces, cagewash), tissues (surrounding skin, treated skin, untreated skin, carcass, blood), stratum corneum (including first two tape strips) and the dose site shavings (including razor blade extract). The dermal absorption value selected was based on the low dose at 168 hours.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/ Loader/ Applicator Exposure and Risk Assessment

Individuals have potential for exposure to isofetamid during mixing, loading and application. Dermal and inhalation exposure estimates for workers were generated from Pesticide Handlers Exposure Database (PHED), Agricultural Handler Exposure Task Force (AHETF) and Outdoor Residential Exposure Task Force (ORETF) databases.

Exposure to farmers and custom applicators mixing, loading and applying Isofetamid 400SC Fungicide is expected to be short to intermediate term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying Isofetamid 400SC Fungicide to grapes, lettuce, rapeseed (canola), low growing berries and turf using airblast, groundboom, backpack, manually-pressurized handwand and turf-gun sprayers. The exposure estimates are based on mixers/loaders/applicators wearing a long-sleeved shirt, long pants and chemical-resistant gloves.

As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures for workers mixing, loading and applying by groundboom, backpack and manually-pressurized handwand sprayers were estimated using the PHED, version 1.1. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. In addition, mixing, loading and applying by turf-gun sprayer was estimated using the ORETF data and application data for airblast sprayers was estimated with AHETF data (Table 3.4.2.1.1).

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAELs; no observed adverse effects levels) to obtain the margin of exposure (MOE); the target MOE is 300. The MOEs for mixers/loaders and applicators were above the target for dermal and inhalation exposure, and therefore, occupational risk associated with mixing/loading and applying Isofetamid 400SC Fungicide is not of concern with the personal protective equipment specified on the label. The exposure and risk estimates are presented in Table 3.4.2.1.2.

Table 3.4.2.1.1 PHED/AHETF/ORETF unit exposure estimates for mixer/loader and applicator while handling Isofetamid 400SC Fungicide

PPE: Single layer plus gloves		Unit exposures (µg/kg ai handled)			
		Dermal	Dermal absorbed[a]	Inhalation[b]	Total unit exposure[c]
Mixer/loader unit exposures					
A	Open pour mixing/loading a liquid, (Scenario 3a)	51.14	6.65	1.6	8.25
Applicator unit exposures					
B	Application using groundboom sprayer (Scenario 11)[d]	32.98	4.29	0.96	5.25
C	Application using airblast sprayer (AHETF Open Cab Airblast Memo)[e]	3769.3	490.0	9.08	499.1
Mixer/loader + applicator unit exposures					
A+B	Open pour mixing/loading, application using groundboom sprayer	84.12	10.9	2.56	13.5
A+C	Open pour mixing/loading, application using airblast sprayer	3820.44	496.7	10.68	507.3
D	Liquid Open Pour / manually pressurized Handwand (Scenario 21a)	943.37	122.6	45.20	167.8
E	Liquid Open Pour / Backpack (Scenario 23a)	5445.85	708.0	62.1	770.1
F	Turf gun (OMA002)[g]	785	102.1	4.0	106.1

[a] Adjusted with dermal absorption factor 13%
[b] Light inhalation rate, except for backpack sprayers (moderate)
[c] Total unit exposure: Dermal absorbed exposure + inhalation exposure
[d] Groundboom application unit exposure for single layer and no gloves (higher confidence data).
[e] AHETF value: Airblast applicator PPE without a chemical resistant hat.
[g] ORETF value: Low pressure nozzle gun sprayer connected to a truck with an 871 L tank

Table 3.4.2.1.2 Chemical handler risk assessment for Isofetamid 400SC Fungicide for workers wearing a single layer and chemical-resistant gloves

Grapes	Unit exposure (µg/kg a.i. handled)	ATPD (ha/day)†	Rate (kg ai/ha)	Daily exposure (mg/kg bw/day)‡	MOE¶
Airblast	507.3	20	0.644	0.0817	1224
Manually pressurized handwand	167.8	3	0.644	0.00405	24671
Backpack	770.1	3	0.644	0.0186	5377

† Default area treated per day; 150 L applied per day for backpack and handwand with minimum water volume of 50 L/ha
‡ Daily exposure = (unit exposure x ATPD x rate) / (80 kg bw x 1000 µg/mg)
¶ Based on NOAEL = 100 mg/kg bw/day, target MOE = 300

Lettuce	Unit exposure (µg/kg a.i. handled)	ATPD (ha/day)†	Rate (kg ai/ha)	Daily exposure (mg/kg bw/day)‡	MOE¶
Groundboom – farmer/custom	13.5	26	0.360	0.00158	63332
Manually pressurized handwand	167.8	3	0.360	0.00227	44134
Backpack	770.1	3	0.360	0.0104	9619

† Default area treated per day; 150 L applied per day for backpack and handwand in minimum water volume of 50 L/ha

‡ Daily exposure = (unit exposure x ATPD x rate) / (80 kg bw x 1000 µg/mg)

¶ Based on NOAEL = 100 mg/kg bw/day, target MOE = 300

Rapeseed (canola)	Unit exposure (µg/kg a.i. handled)	ATPD (ha/day)†	Rate (kg ai/ha)	Daily exposure (mg/kg bw/day)‡	MOE¶
Groundboom - farmer	13.5	107	0.350	0.00632	15829
Groundboom - custom	13.5	360	0.350	0.0213	4705

† Default area treated per day

‡ Daily exposure = (unit exposure x ATPD x rate) / (80 kg bw x 1000 µg/mg)

¶ Based on NOAEL = 100 mg/kg bw/day, target MOE = 300

Low growing berries	Unit exposure (µg/kg a.i. handled)	ATPD (ha/day)†	Rate (kg ai/ha)	Daily exposure (mg/kg bw/day)‡	MOE¶
Groundboom – farmer/custom	13.5	26	0.496	0.00218	45967
Manually pressurized handwand	167.8	3	0.496	0.00312	32033
Backpack	770.1	3	0.496	0.0143	6982

† Default area treated per day; 150 L applied per day for backpack and handwand with minimum water volume of 50 L/ha

‡ Daily exposure = (unit exposure x ATPD x rate) / (80 kg bw x 1000 µg/mg)

¶ Based on NOAEL = 100 mg/kg bw/day, target MOE = 300

Turf	Unit exposure (µg/kg a.i. handled)	ATPD (ha/day)†	Rate (kg ai/ha)	Daily exposure (mg/kg bw/day)‡	MOE¶
Groundboom – golf course	13.5	16	0.636	0.00172	58253
Groundboom – sod farm	13.5	30	0.636	0.00322	31068
Turf sprayer gun	106.1	2	0.636	0.00169	59305

† Default area treated per day

‡ Daily exposure = (unit exposure x ATPD x rate) / (80 kg bw x 1000 µg/mg)

¶ Based on NOAEL = 100 mg/kg bw/day, target MOE = 300

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers entering areas treated with Isofetamid 400SC Fungicide when performing activities such as scouting, transplanting, hand harvesting, etc. The duration of exposure is considered to be short to intermediate term for all activities. The primary route of exposure for workers entering treated areas would be through the dermal route. Inhalation exposure is not considered to be a significant route of exposure for people entering treated areas compared to the dermal route, since active ingredient is relatively non-volatile (vapour pressure is 4.2×10^{-10} kPa at 25°C) and as such, a risk assessment was not required.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values or turf transferable residue values with activity-specific transfer coefficients (TCs). Transfer coefficients are based on data Agricultural Re-entry Task Force (ARTF) data.

Three chemical-specific dislodgeable foliar residue (DFR) and three turf transferable residue (TTR) data were submitted. Reviews of the DFR and TTR studies indicated that they are acceptable and no major limitations were evident.

The three DFR studies were performed on apples, grapes and beans, each at three locations in the United States. For the grape study, application of a 400 g ai/L isofetamid solution was by airblast equipment applied at 652 g ai/ha with a 9-11 day retreatment interval. Samples were collected prior to the first application, just prior to the third (final) application and up to 35 days following the 3rd application. The grape DFR study location with the highest peak DFR was used in the estimation of postapplication exposure in grapes. For the bean study, application of a 400 g ai/L isofetamid solution was by handheld boom or backpack sprayers applied at 500 g ai/ha with a 10-11 day retreatment interval. Samples were collected prior to the second application and up to 35 days after the second (final) application. The bean DFR study location with the highest peak DFR was used in the estimation of postapplication exposure in lettuce, rapeseed (canola) and low growing berries as the application method was equivalent and the leaf type was smooth for beans, lettuce, rapeseed (canola) and low growing berries. Since apple trees or other waxy leaf crops are not on the label, the apple DFR study was not used in the assessment.

The turf transferable residue (TTR) studies were performed on three grass varieties (Bermuda, blue and fescue) and cover three separate regions in the United States: Arkansas, Pennsylvania and North Carolina. Application of a 400 g ai/L isofetamid solution was performed with tractor mounted or backpack CO_2 sprayers at 508 g ai/ha with a 13-15 day retreatment interval. TTRs were assessed using the Modified California Roller (cloth transfer) method prior to the first application; 1 hour and 7 and 14 days after application one; 1 hour and 7 and 14 days after the second application; and 1 hour, 8 hours and 1, 2, 3, 5, 7, 14 and 21 days following the third (final) application. The TTR study from Pennsylvania was selected for estimation of transferable turf residues as this location was most representative of the Canadian use pattern.

Exposure estimates were compared to the toxicological endpoint to obtain the margin of exposure (MOE); the target MOE is 300. The MOEs for workers entering treated fields were above the target for dermal exposure, and therefore, occupational risk associated with postapplication exposure to isofetamid is not of concern with the restricted entry interval specified on the label. The exposure and risk estimates are presented in Table 3.4.2.2.1.

Table 3.4.2.2.1 Postapplication exposure and risk estimates

Activity	Rate ($\mu g/cm^2$)	Peak DFR/TTR ($\mu g/cm^2$) [1]	Transfer coefficient (cm^2/hr) [2]	REI	Dermal exposure (mg/kg bw/day) [3]	MOE [4]
Grapes						
Transplanting	6.44	1.47	230	1 hr	0.00439	22778
Scouting, pruning, hand weeding, propagating, bird control, trellis repair	6.44	1.47	640	1 hr	0.0122	8186
Irrigation (hand set)	6.44	1.47	1750	1 hr	0.0334	2994
Tying/Training, hand harvesting, leaf pulling	6.44	1.47	8500	1 hr	0.162	616
Girdling, turning	6.44	1.47	19300	1 hr	0.368	271
Girdling, turning	6.44	1.35	19300	8 hr	0.339	295
Girdling, turning	6.44	1.19	19300	1 day	0.299	335
Lettuce						
Hand weeding, thinning	3.60	1.11	70	1 hr	0.0010	98662
Scouting	3.60	1.11	210	1 hr	0.0030	32887
Transplanting	3.60	1.11	230	1 hr	0.0033	30028
Hand harvesting	3.60	1.11	1100	1 hr	0.0159	6278
Irrigation (hand set)	3.60	1.11	1750	1 hr	0.0253	3946
Canola						
Scouting	3.50	1.08	1100	1 hr	0.0155	6458
Low growing berries						
Hand weeding, hand pruning	4.96	2.10	70	1 hr	0.0019	52364
Scouting strawberries	4.96	2.10	210	1 hr	0.0057	17455
Scouting lowbush blueberries	4.96	2.10	1100	1 hr	0.0300	3332
Transplanting	4.96	2.10	230	1 hr	0.0063	15937
Hand harvesting	4.96	2.10	1100	1 hr	0.0300	3332
Irrigation (hand set)	4.96	2.10	1750	1 hr	0.0477	2095
Turf						
Aerating, fertilizing, hand pruning, mechanical weeding, scouting, seeding	6.36	0.0899	1000	1 hr	0.0012	85522
Mowing, watering, cup changing, irrigation repair, grooming	6.36	0.0899	3500	1 hr	0.0041	24435
Transplanting/planting,	6.36	0.0899	6700	1 hr	0.0078	12765

harvesting slab						

[1] Based on DFR/TTR study data extrapolated to the maximum application rate and number of applications identified on the label.
[2] Transfer coefficients obtained from ARTF.
[3] Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × 8 hours × dermal absorption) / (80 kg bw × 1000 µg/mg)
[4] Based on a NOAEL of 100 mg/kg bw/day, target MOE = 300.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

Isofetamid 400SC Fungicide is not a domestic product; therefore, a residential handler assessment was not required.

3.4.3.2 Postapplication Exposure and Risk

There is potential for postapplication exposure to the general population entering areas treated with Isofetamid 400SC Fungicide. Although Isofetamid 400SC Fungicide is not for use on residential turf, it is used on golf courses where children, youth and adults may enter. The duration of exposure is considered to be short to intermediate term for golfing. The primary route of exposure for these individuals would be through the dermal route. Isofetamid is considered non-volatile and it is not an inhalation concern for postapplication exposure.

Dermal exposure to golfers is estimated by coupling the TTR value with the transfer coefficient for golfing and the exposure duration of 4 hours per day. Adult (16+ years) and youth (age 11-16 years) risk was calculated using a short- to intermediate-term dermal endpoint (NOAEL) of 100 mg/kg bw/day; target MOE = 300 and child (age 6-11 years) risk was calculated using a short- to intermediate-term dermal endpoint (NOAEL) 1000 mg/kg bw/day; target MOE = 100. Table 3.4.3.2.1 presents the calculated MOE on the day of application, which is above the target MOE for adult, youth and child golfers.

An aggregate (chronic dietary and dermal exposure) risk assessment was not conducted for golfers since the exposure from the chronic dietary toxicity and the studies selected to represent short to intermediate dermal exposure could not be combined.

Table 3.4.3.2.1 Postapplication exposure and risk estimates for golfers entering golf courses treated with Isofetamid 400SC Fungicide

Activity	Rate (µg/cm^2)	Peak TTR (µg/cm^2) [1]	Transfer coefficient (cm^2/hr) [2]	Body weight (kg)	REI	Dermal exposure (mg/kg bw/day) [3]	MOE [4]
Golfing							
Adult	6.36	0.0899	5300	80	1 hr	0.00310	32289
Youth	6.36	0.0899	4400	57	1 hr	0.00361	27711
Child	6.36	0.0899	2900	32	1 hr	0.00424	236042

[1] Based on TTR study data extrapolated to the maximum application rate and number of applications identified on the label.
[2] Transfer coefficients obtained from ARTF Transfer Coefficients.

[3] Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × 4 hours × dermal absorption) / (bw × 1000 µg/mg)
[4] Adult and Youth: Based on a NOAEL of 100 mg/kg bw/day, target MOE = 300.
Child: Based on a NOAEL of 1000 mg/kg bw/day, target MOE = 100.

Given that strawberries, blueberries and other low growing berries can be treated with Isofetamid 400SC Fungicide, there is potential for acute exposure to isofetamid for the general population during pick-your-own (PYO) harvesting activities. However, the hand harvesting assessment (Table 3.4.2.2.1) for workers, which included females 13+ years of age, is protective of the dermal exposure expected for individuals harvesting in PYO operations, as the exposure duration is expected to be 2 hours (vs. 8 hr for workers).

Aggregation of acute dietary and dermal exposure from PYO activities was not conducted, as the risk estimated for each individual route of exposure was well below the level of concern and therefore protective of this scenario. In addition, acute toxicity was not of concern for incidental acute oral exposure for toddlers in relation to hand-to-mouth or soil ingestion activities in the field.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for enforcement in plant products and animal commodities is isofetamid. The residue definition for risk assessment in plant products is isofetamid and the metabolite GPTC. The residue definition for risk assessment in ruminant commodities is isofetamid and the metabolite PPA. The residue definition for risk assessment in poultry commodities is isofetamid. The data gathering/enforcement analytical method is valid for the quantitation of isofetamid and GPTC residues in crop matrices. The data gathering analytical method is valid for the quantitation of isofetamid and PPA residues in animal matrices. The residues of isofetamid and GPTC are stable in representative matrices from five crop categories [almonds and canola (high oil), grapes (high acid), lettuce (high water), potatoes (high starch) and dry beans (high protein)] for up to 12 months when stored in a freezer at ~ -20°C. Therefore, isofetamid and GPTC residues are considered stable in all frozen crop matrices and processed crop fractions for up to 12 months. Isofetamid residues concentrated in the following processed commodities: raisins (2.3×), and canola oil (2.0×). Quantifiable residues are not expected to occur in livestock matrices with the current use pattern. Crop field trials conducted throughout Canada and/or the United States using end-use products containing isofetamid at approved (or exaggerated) rates in or on grapes, lettuce, strawberry, canola and almond are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic non-cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.16), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic/intermediate chronic non-cancer analysis for isofetamid: 100% crop treated, default and experimental processing factors (where available), and residues of grape, strawberry, lettuce, canola and almond based on supervised trial median residue (STMdR) values. The intermediate chronic dietary exposure from all supported isofetamid food uses (alone) for the total population, including infants and children, and all representative population subgroups is 0.6% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to isofetamid from food and drinking water is 2% (0.000990 mg/kg bw/day) of the ADI for the general population. The highest exposure and risk estimate is for all infants (< 1 year) at 5% (0.00239 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for isofetamid: 100% crop treated, default processing factors, and residues in/on crops commodities at MRL levels. The basic acute dietary exposure (food alone) for all supported isofetamid registered commodities is estimated to be 4% (0.01185 mg/kg bw/day) of the ARfD for females 13–49 years old (95th percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: 5% (0.0145 mg/kg bw/day) of the ARfD for females 13–49 years old.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for isofetamid consists of exposure from food and drinking water sources as well as residential uses (golf). For details concerning golfer exposure, refer to Section 3.4.3.

Furthermore, given that strawberry or other low growing berries can be treated with isofetamid, there is potential for aggregate exposure to isofetamid during pick-your-own activities. The acute dietary assessment for female 13+ is protective of the acute exposure from eating berries during pick-your-own activities. Aggregation of acute dietary and dermal exposure from PYO activities was not conducted as the risk estimated for each individual route of exposure was well below the level of concern and therefore, protective of this scenario.

3.5.4 Maximum Residue Limits

Table 3.5.4.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Leaf Lettuce	7
Head lettuce, raisins	5
Crop Subgroup 13-07G, Low growing berry	4
Crop Subgroup 13-07F, Small fruit vine climbing , except fuzzy kiwifruit	3
Canola oil, flaxseed oil, mustard seed oil, sesame oil	0.03
Crop Subgroup 20A, Rapeseed (Revised)	0.015
Almond Nuts	0.01*

* Proposed for import commodities.

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of Health Canada's website.

For additional information on Maximum Residue Limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 5 and 6.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

In the terrestrial environment, isofetamid undergoes biotransformation resulting in several minor transformation products. According to submitted environmental fate data, isofetamid is expected to be moderately persistent in soils. In laboratory soil studies isofetamid was transformed primarily by microbial degradation. In aerobic soils the half-lives ranged from 25 – 66 days and although the half-life was somewhat longer for soil temperatures less than 20°C the persistence classification remained moderate for aerobic soils. Isofetamid can persist for greater than six months but less than one year under anaerobic conditions and is also classified as moderately persistent in anaerobic soils. Phototransformation is not expected to be a major route of dissipation of isofetamid on soil. In two field studies where isofetamid was applied to bare soil in Canadian-equivalent U.S. ecozones and isofetamid residues remained in the soil at the beginning of the following growing season ranging from 9 – 15.3% of the highest measured residues. Faster dissipation times were observed in field trials conducted on cropped sites in the United States. As the proposed use pattern involves application to crops, the results of the cropped plot study conducted in the southern U.S. may be indicative of slightly faster than predicted dissipation of isofetamid applied to crops versus bare soil under Canadian conditions.

Isofetamid sorbs moderately or strongly to soil depending on levels of soil organic carbon. According to the soil mobility classifications of McCall et al.(1981) and Cohen et al. (1984) isofetamid is classified as having low to moderate mobility and is not expected to move into or leach into ground water, depending on the permeability and organic matter content of the soil. Isofetamid may reach surface water through runoff through sorption to soil particles. Criteria for these classifications include:

- K_{oc} of 150 – 500 (moderate mobility) and 500-2000 (low mobility) (K_{oc} of IFM is 281 – 615, depending upon soil organic carbon content)
- solubility in water > 30 mg/L (IFM solubility in water is 5.33 mg/L at pH 7)
- Henry's Law Constant of $<10^{-2}$ atm-m^3/mol (Henry's Law Constant for IFM = $2.7E^{-8}$ atm-m^3/mol)
- Negatively charged (either fully or partially) at ambient pH (IFM does not dissociate at environmentally relevant pH values)
- Hydrolysis half life >20 weeks (IFM is stable to hydrolysis)
- Photolysis half life > 1 week (IFM aqueous photolysis 1.8 days, stable to photolysis in soil, half-life 267 days)
- Half life in soil > 2-3 weeks (IFM half life in aerobic soil 22 - 55 days, IFM half life in anaerobic soil is 572 days or *ca* 82 weeks)

The method of Gustafson (1989) may also be used to estimate the leaching potential of pesticides. Gustafson's assessment method uses a groundwater ubiquity score (GUS), which is based on the persistence and mobility of the compound and is expressed as:

$$GUS = \log_{10}(t_{1/2\,soil}) \times (4 - \log_{10}(K_{oc}))$$

The GUS value indicates the leachability of the compound. The persistence term in the GUS equation, $t_{1/2\,soil}$, is the field dissipation time (DT_{50}) as determined in field dissipation studies, and is meant to include dissipation by volatilisation, phototransformation, and biological transformation. Instead of the field dissipation DT_{50}, however, the laboratory aerobic soil DT_{50} or $t_{1/2\,soil}$ values will be used in the GUS equation; this is because the field dissipation value may also include dissipation from leaching and runoff and therefore, may underestimate leaching potential when used in the equation. The GUS classification scheme is as follows:

Leachability Classification System based on GUS indices

GUS	Probability Attributes
>2.8	Leacher
>1.8 and <2.8	Borderline leacher
<1.8	Non-leacher

The lowest Koc value (281.1 mL/g in SK961089 clay soil) and the shortest aerobis soil biotransdformation half-life (24.5 days) was used to calculate the GUS score in order to represent the most conservative scenario for GUS leachability. The GUS values calculated for isofetamid using these parameters was 2.15 which would classify isofetamid as a borderline leacher.

Isofetamid is moderately to highly adsorptive on soils and is not expected to readily leach to groundwater. Isofetamid was not found at soil depths below 15 cm in field dissipation studies that were conducted in regions relevant to Canada (Saskatchewan and North Dakota).

In laboratory aerobic and anaerobic soil studies, 4-HP was identified as one of a number of minor transformation products and reached a maximum of 9.2% of the applied parent at 30 days after treatment in the aerobic soil study and 9.5% of the applied parent at 150 days after treatment in the anaerobic soil study. By contrast, 4HP was identified as a major transformation product in terrestrial field dissipation studies conducted in on bare soil in Saskatchewan and the northern United States (North Dakota) and on turf in the southern United States (North Carolina). 4-HP is expected to be persistent in aerobic soil although the potential for the formation and/or accumulation of 4-HP is expected to be low because at the end of the relevant studies, residues of the transformation product 4-HP were not detected. In terrestrial field dissipation studies 4-HP was the only transformation product identified. Laboratory adsorption data for 4-HP indicate that 4-HP is expected to be moderately mobile although in relevant studies, 4-HP was detected sporadically in the 0-15 cm soil layer at measurable concentrations but was not detected in the soil below depths of 15 cm. Therefore, 4-HP is not expected to readily leach to groundwater.

Isofetamid has low aqueous solubility. Based on its low vapour pressure and Henry's Law Constant, volatilization of isofetamid from moist soil or water surfaces is unlikely to be a significant route of dissipation in the environment.

In the aquatic environment, isofetamid is considered stable to hydrolysis at environmentally relevant pH values and therefore, hydrolysis is not expected to be a significant route of transformation in most agricultural area waterbodies. Isofetamid will undergo rapid photolysis in shallow, clear waters, and it is likely that the majority of the substance undergoes photolysis before partitioning out of the photic zone and into sediments or other organic matter. In deeper water, aerobic and anaerobic biotransformation is not expected to be an important route of transformation. Depending upon the sediment type, isofetamid is expected to bind either strongly or moderately to aquatic sediment and/or suspended particles based on its soil/water partitioning coefficients. Isofetamid is moderately persistent and persistent in aerobic and anaerobic aquatic systems, respectively, therefore, prolonged exposure of aquatic organisms to isofetamid may occur under the proposed use-pattern.

Isofetamid is not expected to bioaccumulate in biota, as the log K_{OW} value is less than 2.5 at environmentally relevant pH values. Data related to the environmental fate of isofetamid and its major transformation products are found in Appendix 1, Table 7 and 8. The transformation pathways for isofetamid in aerobic soil and in water are summarized in Figure 1 and Figure 2 of Appendix 1.

Overall, the primary routes of dissipation in the terrestrial environment are plant uptake, microbially-mediated degradation in aerobic soils and adsorption to soil particles. In the aquatic environment, the main route of dissipation is expected to be sorption to sediments and photolysis in shallow, clear waters and sorption to aquatic sediments in deeper waters. Isofetamid residues are not expected in the atmosphere, and long range atmospheric transport is not expected.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

Risks from isofetamid and its related end use product, Isofetamid 400SC, were assessed based upon the use pattern for the end-use product and the evaluation of toxicity data for the following surrogate species (Appendix I, Table 9):

- One earthworm species, one bee species, two other arthropods representing invertebrates
- Three bird and one mammal species representing vertebrates
- 11 crop species representing vascular plants

The screening level RQs for Isofetamid 400SC were assessed using EECs as described below.

Soil EECs, were used as screening level estimates to assess the potential risk to soil dwelling organisms, and will be estimated assuming 100% deposition of the spray application to soil, a soil density of 1.5 g/cm^3, and even incorporation of residues in soil to a depth of 15 cm. Soil EECs were used to model exposure to earthworms as soil is assumed to be the primary route of exposure (ingestion and contact).

To assess the potential risk of isofetamid to non-target plants, screening level exposure estimates were based on the proposed maximum application rates. Due to the low vapour pressure of isofetamid, volatilization is an unlikely source of non-target plant exposure. Therefore, screening level assessments for runoff and spray drift routes of exposure were considered for estimation of the isofetamid EECs for terrestrial and semi-aquatic plants.

Exposure estimates on potential foods items for assessing risk to terrestrial organisms were determined based on the EPA nomogram (Hoerger and Kenaga 1972 and Kenaga 1973, and Fletcher 1994) using the cumulative application rate which takes into consideration the rate of each application, the number of applications per season, the interval between each application, and a default foliar dissipation half-life of 10 days. For beneficial terrestrial arthropods exposure can occur via direct contact exposure from spray applications as described for bees or through exposure to residues in the soil. Some predators and parasites reside primarily on foliage, while others reside primarily on soil, and thus both will be considered separately for exposure. Estimates for birds and mammals were expressed both in terms of a maximum dietary concentration (ppm) and in terms of the daily dose (mg/kg bw/d) to account for differences in animal feeding rates. Exposure is dependent on the body weight of the organism and the amount and type of food consumed. Therefore, the estimated daily exposure (EDE) was based on a set of generic body weights to represent a range of species (20, 100, 1000 g for birds and 15, 35, 1000 g for small mammals).

For estimating screening level contact exposure to bees the contact toxicity endpoint was converted to field rate as per Koch and Weiber 1997, using the maximum single application rate in kg × 2.4 µg a.i./bee per 1 kg a.i./ha which yields an EEC of 1.56 kg a.i./ha (0.644 kg a.i./ha × 2.4 µg a.i./bee per 1 kg a.i./ha). The oral exposure estimate for adult bees was calculated by multiplying the highest single application rate (0.644 kg a.i./ha on grapes) by 29 µg a.i./bee per kg/ha. This conversion is based on nectar consumption rates for forager bees primarily derived from Rortais et al (2005) and Crailsheim et al (1992 and 1993).

4.2.2 Risks to Terrestrial Organisms

Effects of isofetamid on terrestrial species were based upon the evaluation of toxicity data reviewed for earthworms (short term), honeybees (short term), two beneficial arthropods (short term), three birds species (short term and reproductive), and eleven plant species (seedling emergence and vegetative vigour) (Appendix I, Table 9).

Isofetamid is classified as relatively non-toxic to earthworms, honeybees and beneficial terrestrial arthropods. Isofetamid is classified as relatively non-toxic to birds and mammals on an acute toxicity basis, although results from the reproductive studies for bobwhite quail showed reductions in overall reproductive success (reduced number of normal hatchlings) at ingestion levels above 25 mg a.i./kg-bw and eggshell thinning at ingestion levels of ≥ 119 mg/kg bodyweight/day in males and 121 mg/kg bodyweight/day in females for mallard duck. No treatment related effects were observed for terrestrial plants except for corn and tomato (seedling germination). There were no significant reductions in emergence or survival for any other species at any treatment level compared to the negative control.

A screening level risk assessment for earthworms, honeybees, predators and parasites, birds, small mammals and terrestrial plants was conducted as these organisms may be exposed through direct application, contact with treated material or from ingestion of contaminated food. The calculated screening level risk quotients for terrestrial organisms are summarized in Table 10 and were calculated using the EECs as described below and ecotoxicology endpoints in Table 9. The EECs are based on the Isofetamid 400SC application rate of eight applications of 638 g a.i./ha, a 14 day interval, and a either a soil half-life of 66.2 days, or a default foliar half-life of 10 days. Where applicable, the assessment was based on the assumption that the diet consists entirely of food sources contaminated with isofetamid. In addition, it was also assumed that non-target plants and avian and mammalian food sources outside of the treated field were at least 1 m downwind from the last spray swath and would therefore only be exposed to 6% of the expected on-field concentrations through spray drift from field-sprayer applications ($EEC_{off\text{-}field} = EEC_{in\text{-}field} \times 0.06$).

Terrestrial Invertebrates

Earthworms: Exposure of earthworms to isofetamid could result from ingestion of treated soil. Earthworms are not expected to be at risk from the application of Isofetamid 400SC at the proposed Canadian use rate. The acute risk to earthworms from isofetamid, at the proposed cumulative application rate (turf) was less than the LOC (Table 10).

Pollinators: According to the classification system of Atkins (1981; LD_{50}>10.99 µg/bee classified as relatively non-toxic; LD_{50} = 2.0-10.99 µg/bee classified as moderately toxic and LD_{50} = 0.001 - 1.99 µg/bee classified as highly toxic), isofetamid is relatively non- toxic to bees on an acute contact (LD_{50} > 100 µg a.i./bee) and oral basis (LD_{50} = 30 µg a.i./bee). Koch and Weiber 1997 investigated potential contact based exposures to pesticides through applications of a fluorescent tracer (sodium-fluorescein) to flowering apple orchards and *Phacelia tanacetifolia* fields located in Germany. Bees were foraging during spray application, so they could have been directly sprayed with the tracer which would represent a worst-case contact exposure. Honey bees are important pollinators and they can be exposed to residues of isofetamid from direct application or contact with treated plant material. The single highest application rate (644 g a.i./ha on grapes) was used as the contact exposure estimate from foliar applications. In order to compare the application rate to the acute contact toxicity endpoint derived in laboratory studies (µg a.i./bee), a conversion from kg a.i./ha to µg a.i./bee is required. The proposed upper-bound residue value for estimating exposures to honey bees is based on the maximum residue value reported by Koch and Weiber 1997 (2.4 µg a.i./bee per 1 kg a.i./ha). The estimated residues per bee following a single application of 644 g a.i./ha on grapes is 1.55 µg a.i./bee. A risk quotient (RQ) was calculated by dividing this value by the 48-h contact LD_{50} value of >100 µg a.i./bee.

The oral exposure estimate for adult bees is calculated by multiplying the highest single application rate (0.644 kg a.i./ha on grapes) by 29 µg a.i./bee per kg/ha. This conversion is based on nectar consumption rates for forager bees primarily derived from Rortais et al (2005) and Crailsheim et al (1992 and 1993). Following the conversion, the estimated oral exposure is 18.7 µg a.i./bee based on the single application rate for grapes. A risk quotient (RQ) was calculated by dividing this value by the 48-h oral LD50 value of 30 µg a.i./bee.

The level of concern (LOC) for the Tier 1 acute exposure is 0.4. This value is based on a median slope of 3.2 for the dose response curve from acute contact and oral toxicity studies and a limit of 10% mortality (amount of mortality test guidelines allowed in control groups). The result reported in Table 10 show that the LOC was exceeded slightly (RQ = 0.6) on an acute oral exposure basis. This assessment was based upon the conservative endpoint of >30 ug a.i./bee (TGAI) using the nectar consumption rates from Rortais et al (2005) and Crailsheim et al (1992 and 1993) when the rates for turf and grapes were used. An RQ of 0.5 was calculated for the lower rates on blueberries, strawberries and cranberries (CG-13). The RQs did not exceed the LOC for the other proposed rates/crops. Under the new pollinator risk assessment framework (White Paper, 2012), a risk at the screening level triggers a request for Tier 1 data, either a semi-field study and/or pollen/nectar residue data. In this case, because of the mode of action (not specific to immature growth stages of bees), the fact that the oral endpoint is not a true endpoint but was >30 ug a.i./bee and the endpoint for the end-use product is >100 ug a.i./bee, the Tier 1 or brood data is not required. In addition, the level of concern (LOC) of 0.4 was considered by the Federal Insecticide Fungicide and Rodenticide Act Scientific Advisory Panel to be highly conservative. This LOC was based on an effect level that would be consistent with background (i.e. control mortality) in laboratory-based studies. The LOC was not exceeded for bees exposed to isofetamid residues for the proposed uses on an acute contact toxicity.

Predators and Parasites: Exposure of predators and parasites to isofetamid could result from contact with treated plant material and consumption of contaminated target species treated crop fields. Currently there are no methods to estimate the EEC in the diet for beneficial arthropods and therefore risk is assessed for the short-term contact pathway only. Several studies on the toxicity of the Isofetamid 400SC to predatory arthropods were reviewed (Table 9). From the studies provided, *Aphidus rhopalosiphi* and *Typhlodromus pyri* both had reported LR_{50}'s of >1000 g a.i./ha. Acute (48 h) exposure of parasitoid wasps to isofetamid at EECs based on the cumulative maximum seasonal rate (1026.95 g a.i./ha) resulted in a negligible risk for in-field and off-field exposure (Table 10). Based on mortality observed in *T. pyri*, isofetamid would pose a negligible risk to predatory arthropods in treated fields and areas adjacent to fields. Mitigation measures are therefore not required.

Birds and Wild Mammals

Toxicity to Birds

Available acute toxicity data indicate that isofetamid is practically non-toxic to bobwhite quail (*Colinus virginianus*,) and canaries (*Serinus canaria*,) in oral gavage studies. An oral gavage study conducted with mallard ducks was determined to be invalid due to emetic effects on ten out of the twelve birds. Acute dietary studies conducted with bobwhite quail and mallard duck also indicate that isofetamid is practically non-toxic to birds on an acute basis. Chronic reproductive dietary studies with bobwhite quail and mallard duck indicated isofetamid was toxic to birds on a reproductive basis with NOAECs of 276 and 285 mg a.i./kg diet, respectively. All bird toxicity studies were conducted with isofetamid technical grade active ingredient.

Toxicity to Mammals

The endpoints chosen to represent mammalian toxicity are found in Table 9. For the acute toxicity endpoint, the acute oral toxicity study (gavage) LD_{50} > 2000 mg ai/kg bw in rats was chosen to represent acute toxicity in wild mammals.

For the reproductive effects in mammals the multi-generation reproductive study in rats was chosen to represent the reproductive endpoint for mammals as reproductive effects were found at the 659 mg ai/kg bw/day dose. This endpoint is also protective for the developmental effects found at >300 mg/kg bw/day in (Developmental Toxicity, gavage, Sprague Dawley rats, 22 females/group, 0, 100, 300, 1000 mg/kg bw/day) in which the following effects were observed: visceral malformations in the heart and/or major blood vessels including malrotated heart, narrow pulmonary trunk, dorsally displaced pulmonary trunk, muscular ventricular septal defect, membranous ventricular septal defect, absent ductus arteriosus, ascending aorta/pulmonary trunk fistula and incomplete caudal vena cava with persistent cardinal vein. While the developmental effects observed may be important, there was no information on the incidences and the relationship with the reproductive success of small mammals in the field with these effects is not clear. Therefore, by using the multi-generation reproductive endpoint the effects seen in the developmental study are considered to be covered.

Birds – screening level

Wild upland game birds and waterfowl, could be exposed to residues of isofetamid as a result of consumption of treated vegetation, contaminated prey or spray drift.

Before calculating the risk quotient, toxicity endpoints reported as concentrations (mg a.i./kg diet; such as results from the short-term dietary and long term reproduction studies) were converted to daily doses (mg a.i./kg bw/day). These were determined according to the average food ingestion rate (FIR) and the body weight (BW) for birds observed during the exposure period of the respective toxicity tests according to the following formula: Daily Dose (mg a.i./kg bw/day) = Toxicity endpoint (mg a.i./kg diet) x FIR (kg diet/bird/day) x 1/BW (kg bird).

The screening level risk assessment (Table 11) was based on the maximum seasonal application rate for turf (8 x 638 g a.i./ha, 14 day interval and a 10-day foliar half-life) were converted to an estimated daily exposure (EDE). Exposure is dependent on the body weight of the organism and the amount and type of food consumed, and a set of generic body weights was used in the screening level risk assessment to represent a range of birds (20, 100 and 1000 g). The EDE was calculated using the following formula: (FIR/BW) x EEC. For each bodyweight, the food ingestion rate (FIR) was based on equations from Nagy (1987).

Also, a generic set of food preferences is considered at the screening level: 100% small insects for insectivores, 100% fruits for frugivores, 100% grain and seeds for granivores, and 100% leaves and leafy crops for herbivores. Since no small birds in North America are known to eat a diet primarily of leafy plant material or grass, EDEs for smaller birds (20 and 100g) are based on a 100% diet of plants were not calculated. EDEs for the screening level risk are presented in Table 11.

Risk quotients were calculated by comparing appropriate toxicity endpoints (most sensitive LD_{50} or NOEL, expressed in terms of mg a.i./kg bw/d) to the EDE. At the screening level, the most conservative in-field and off-field EDE for each food guild was used. Also, the acute oral (1 day exposure) and dietary (5 day exposure) toxicity endpoints were divided by a factor of 10 to account for potential differences in species sensitivity as well as varying protection levels (community, population, individual).

Screening-level risk quotients determined for each bird body weight (20 g, 100 g and 1000 g) and feeding guild for isofetamid are shown in Table 11. The on-field risk quotients exceed the level of concern for all sizes of birds on a reproductive basis.

Birds – Further Characterization

Further characterization of risk using mean nomogram residues showed reproductive risk to all feeding guilds of small birds, medium insectivores and frugivores and large herbivores. There was no risk considering either maximum or mean nomogram values to any feeding guild for the off-field scenario. Reproductive risks for on-field exposure were found for small, medium and large sized birds from eating insects and short grass for large birds. Considering that these food items are relevant for turf, further refinement was not attempted as there is a clear risk when considering both the maximum residues and the mean residues which means that adverse effects are likely to occur at a broad range of residue concentrations on food in the field. An appropriate label statement to identify hazard will be added to the Isofetamid 400SC label.

To summarize, there are reproductive concerns for birds from use of isofetamid used on turf at the proposed maximum rate of 638 g a.i./ha and 8 applications spaced at 14 days apart (Table 14).

Mammals – Screening Level – turf applications
Wild mammals could be exposed to residues of isofetamid as a result of consumption of sprayed vegetation and/or contaminated prey.

To characterize the exposure for the risk assessment, the nomogram results based on the maximum seasonal application rates for turf (8 x 644 g a.i./ha, 14 day interval and a 10-day foliar half-life) were converted to an estimated daily exposure (EDE). Because potential exposure is dependent on the metabolic rate of the organism which is related to the organism's body weight, a set of generic body weights is considered (15, 35, 1000 g for mammals). The amount and type of food consumed was also considered by taking into consideration a generic set of food preferences at the screening level: 100% small insects for insectivores, 100% fruits for frugivore, 100% grain and seeds for granivores, and 100% leaves and leafy crops for herbivores. Similarly to birds, a 100% diet of plants for the smallest size of mammal was not included. The EDE was calculated using the following formula: (FIR/BW) x EEC. For each body weight, the food ingestion rate (FIR) was based on equations from Nagy (1987).

Risk quotients were calculated by comparing appropriate toxicity endpoints (most sensitive LD_{50} or NOEL, expressed in terms of mg a.i./kg bw/d) to the EDE. At the screening level, the most conservative EDE for each food guild was used. Also, to account for differences in species sensitivities and protection goals (for example, community, population and individual), the acute toxicity endpoint was divided by an uncertainty factor of 10. Risk quotients determined for each mammal body weight and feeding preference group are shown in Table 12.

The level of concern (LOC) was not exceeded following acute exposure of isofetamid to small, wild mammals (Table 12). Screening level risk quotients calculated based on reproductive endpoints for medium sized mammals consuming grass, however, exceeded the level of concern. Risks from reproductive exposure were based on a NOAEL of 65.8 mg/kg bw/day observed in the two-generation reproductive study conducted on rats via diet. Based on this endpoint, small herbivorous mammals of medium size (35 g) feeding only on short grass could be at risk from isofetamid for on-field exposure. Reproductive risks are not expected in mammals foraging exclusively off-field. A refinement of the on-field and off-field scenarios was conducted.

Mammals – Further Characterization – turf applications
When mean nomogram residues were considered, there were no exceedances of the LOC for either on, or off-field scenarios for medium sized mammals feeding exclusively on grass.
It is expected that mammals will be exposed to a range of concentrations on food but effects are only expected to occur at the highest end of the residue concentration spectrum. Further refinements, such as bracketing the endpoints, were not required.

To summarize, some risk is expected to small, wild mammals via exposure from use of isofetamid on turf at the proposed maximum rate of 638 g a.i./ha and 8 applications spaced at 14 days apart (Table 15). Hazard statements will be required on the product label.

Terrestrial Plants

Non-target terrestrial plants could be exposed to isofetamid through spray drift at the time of application, or as a result of overland runoff of treated soil following a heavy rain event. Currently, risk to non-target plants is determined for spray drift only. Exposure from foliar application of the EP Isofetamid 400SC at levels of up to 1366 g a.i./ha for dicots and 1200 g a.i./ha for monocots did not result in detrimental effects of greater than 25% of the test populations for vegetative vigour studies. Phytotoxic effects affecting greater than 25% of the test population were seen for one dicot species (tomato) in the seedling emergence test at 16.1 mg a.i./kg soil (*ca* 36,250 g a.i./ha), although monocots were not affected at up to 851 mg a.i./kg soil. The expected environmental concentration in soil at the maximum cumulative rate (turf use: 8 applications, 14 days apart at 638 g a.i./ha, soil density = 1.5 g/cm3 , aerobic soil half-life = 66.2 days) is 1.9 mg a.i./kg soil. The expected environmental concentration for vegetative vigour (cumulative application rate) of 1026.95 g a.i./ha was calculated assuming eight applications, each 14 days apart at 638 g a.i./ha (turf), with a half-life on plant surfaces of 10 days. Risk quotients were calculated using the EC25 toxicity values for the most sensitive species from each of the seedling emergence (tomato) and vegetative vigour (soybean) tests. A species sensitivity distribution endpoint was not calculated as the EC50 endpoints for all species save the two most sensitive from each test were greater than the highest application rate used for testing. To conduct a species sensitivity test a distribution of at least four endpoints are required. Risk quotients did not indicate risk to terrestrial plants for seedling emergence or vegetative vigour at the highest cumulative application rate (Table 10).

4.2.3 Risks to Aquatic Organisms

Risks from isofetamid and its related end use product, Isofetamid 400SC, were assessed based upon the use pattern for the end-use product and the evaluation of toxicity data for the following surrogate species (Appendix I, Table 9):

- Four freshwater fish species, one marine fish species
- Two marine aquatic arthropod species, one freshwater pelagic and one benthic arthropod species
- Three freshwater aquatic algae and one marine species and one species of aquatic vascular plants

Mortality was seen in aquatic invertebrates and fish acutely exposed to isofetamid, and is classified as moderately toxic to pelagic aquatic animals. Several groups of aquatic organisms animals are at risk from chronic exposure to isofetamid, including fish, amphibians, and aquatic invertebrates (marine).

Aquatic Exposure - Screening Level

Screening level EEC values for isofetamid in water were calculated assuming a reasonable conservative scenario of direct application to water bodies of two different depths (80 cm and 15 cm). The 80-cm water body is chosen to represent a permanent body of water and 15 cm is chosen to represent a seasonal body of water. The permanent body of water will be used to assess

the risk to organisms that depend on it all year such as fish; whereas the seasonal body of water will be used to assess the risk to organisms that use seasonal bodies of water such as amphibians. The screening level calculation is intended to be a simple, conservative estimate of isofetamid concentration in a surface water body. This initial level of assessment is designed to effectively screen out pesticides or uses that are unlikely to pose a risk to the aquatic environment. The pesticide is assumed to be instantaneously and completely mixed within the water body. Based on eight applications, spaced 14 days apart of 638 g a.i./ha and assuming the longest total aquatic system half-life of 174.7 days (at 20 degrees Celsius) the EECs are 0.53 mg a.i./L (permanent water body 80 cm in depth) and 2.82 mg a.i./L (seasonal water body 15 cm in depth).

For groups where the LOC is exceeded, a refined Tier I assessment was conducted to determine risk resulting from spray drift and runoff separately.

Aquatic Ecoscenario Assessment - Level 1 Modelling

For Level 1 aquatic ecoscenario assessment, estimated environmental concentrations (EECs) of isofetamid from runoff into a receiving water body were simulated using the PRZM/EXAMS models. The PRZM/EXAMS models simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. For the Level 1 assessment, the water body consists of a 1 ha wetland with an average depth of 0.8 m and a drainage area of 10 ha. A seasonal water body was also used to assess the risk to amphibians, as the risk quotient for amphibians exceeded the level of concern at the screening level. This water body is essentially a scaled down version of the permanent water body noted above, but having a water depth of 0.15 m. Pore water concentrations were also generated for isofetamid in a water body 0.8 m deep.

Seven standard regional scenarios were modelled to represent different regions of Canada. Various initial application dates between May and August were modelled for each region of Canada and use pattern. The EECs are for the portion of the pesticide that enters the water body via runoff only; deposition from spray drift is not included. The models were run for 50 years for all scenarios.

The EECs are calculated from the model output from each run as follows. For each year of the simulation, PRZM/EXAMS calculates peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the daily concentrations over five time periods (96-hour, 21-day, 60-day, 90-day, and 1 year). The 90^{th} percentiles over each averaging period are reported as the EECs for that period.

The largest EECs of all selected runs of a given use pattern for all regional scenarios are reported in Tables 4.2.2.1 and 4.2.2.2 for overlying water in water bodies 0.15 m and 0.8 m deep, respectively, and in Table 4.2.2.3 for pore water in a water body 0.8 m deep.

Table 4.2.3.1: Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for isofetamid in the overlying water of a water body 0.15 m deep, excluding spray drift.

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Turf use, 8 × 638 g a.i./ha, at 14-day intervals						
Prairies	99	64	28	20	19	13
Ontario	82	54	25	19	17	12
Quebec	72	46	24	18	16	11
Grapes use, 3 × 644 g a.i./ha, at 14-day intervals						
British Columbia	14	8.8	3.6	2.4	2.1	1.4
Berries use (excluding grapes), 5 × 496 g a.i./ha, at 7-day intervals						
Ontario	169	111	65	47	46	34
Quebec	145	98	53	50	47	36
Atlantic	334	240	148	116	105	70

Table 4.2.3.2 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for isofetamid in the overlying water of a water body 0.8 m deep, excluding spray drift.

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Turf use, 8 × 638 g a.i./ha, at 14-day intervals						
Prairies	22	20	16	14	13	9.1
Ontario	19	18	15	13	12	8.6
Quebec	17	17	14	12	11	7.7
Grapes use, 3 × 644 g a.i./ha, at 14-day intervals						
British Columbia	2.9	2.7	2.0	1.6	1.6	1.1
Berries use (excluding grapes), 5 × 496 g a.i./ha, at 7-day intervals						
Ontario	50	47	38	33	32	24
Quebec	42	40	35	33	32	25
Atlantic	102	97	89	80	75	51

Table 4.2.3.3 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for isofetamid in pore water of a water body 0.8 m deep, excluding spray drift.

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Turf use, 8 × 638 g a.i./ha, at 14-day intervals						
Prairies	12	12	12	12	12	8.7
Ontario	12	12	12	12	12	8.4
Quebec	11	11	11	10	10	7.8
Grapes use, 3 × 644 g a.i./ha, at 14-day intervals						

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
British Columbia	1.7	1.7	1.7	1.6	1.6	1.1
Berries use (excluding grapes), 5 × 496 g a.i./ha, at 7-day intervals						
Ontario	31	31	31	31	30	24
Quebec	31	31	31	31	30	25
Atlantic	72	72	71	70	68	52

Tier 1 EECs - Summary

Refined EECs for spray drift are expected to be 0.0318 mg a.i./L in 80 cm water depth and 0.169 mg a.i./L in 15 cm depth (refer to Table 4.2.2.4) based upon the cumulative rate for turf use (8 applications of 638 g a.i./ha, spaced 14 days apart). Refined EECs from overland runoff sources are shown in Table 4.2.2.5. These represent the greatest potential for risk based on the proposed use pattern and site characteristics for use on berries in Atlantic Canada.

Table 4.2.3.4 Refined Tier I aquatic EECs for Isofetamid based on spray drift input only, assuming a 1 m distance between sprayer and aquatic habitat.

Sprayer Type	% Drift at 1 m (based on ASAE Medium spray quality)	EEC (mg a.i./L)	
		Non-permanent/ shallow water bodies (15 cm deep)	Permanent water bodies (80 cm deep)
Field sprayer (ground boom)	6	0.169	0.0318

Table 4.2.3.5 Aquatic EECs used for Tier 1 Refinement – Overland Run-off

		EEC mg a.i./L from runoff sources (w/ duration)	
Toxicity study duration	Water body depth (cm)	Overlying water	Porewater
Acute (48 – 120 h)	15	0.24 (96 h)	n/a
	80	0.097 (96 h)	0.072 (96 h)
Chronic (21 – 28 d)	15	0.148 (21 d)	n/a
	80	0.089 (21 d)	0.071 (21 d)

Effects of isofetamid on aquatic organisms were based upon evaluation of toxicity data for fourteen species. Effects on marine aquatic organisms were based on review of studies for four saltwater species representing marine invertebrates, marine algae and marine fish. Effects on freshwater aquatic species were based on review of three freshwater algae species (short term), one aquatic plant species (short term), four freshwater fish species (short and long term) and two freshwater aquatic invertebrate species (short and long term) (Appendix I, Table 9).

Screening Level Aquatic Risk Assessment

Aquatic organisms can be exposed to isofetamid as a result of spray drift and over-land run-off. To assess the potential for adverse effects, screening level EECs in the aquatic environment based on a direct application to water were used as the exposure estimates. The toxicity endpoints and uncertainty factors used in modifying the toxicity values are summarized in Table 13.

In the freshwater environment, isofetamid has no risk of acute effects to invertebrates, benthic invertebrates, algae or vascular plants. Isofetamid exhibited acute toxic effects to fish on an acute and chronic basis and to aquatic invertebrates on a chronic basis (Table 16).

In the marine environment, isofetamid poses an acute risk to fish, aquatic invertebrates, mollusks and algae (Table 16).

To assess the risk to amphibians for acute and chronic exposure, the toxicity values for the most sensitive fish species were used as surrogate data along with the EEC in a 15 cm deep body of water. The screening level risk quotients exceeded the level of concern for amphibians on an acute and chronic basis (Table 16).

Fish

Freshwater fish: The risk from acute toxicity of isofetamid was determined for three species of fish (rainbow trout, bluegill sunfish, and common carp) and the risk from chronic toxicity was determined for the fathead minnow. The risk quotients were calculated using one or the other of the following formulas: for an acute exposure: RQ = EEC in an 80-cm deep water body / (LC50 ÷ 10), or for a chronic exposure: RQ = EEC in a 80-cm deep water body / NOEC. For all acute and chronic studies, risk quotients were > 1. In the case of the Bluegill sunfish, the endpoint used to determine risk (LC50) was not a true endpoint as effects on 50% of the population were not observed in acute studies (Table 13). A Tier 1, refined chronic risk to fish was determined for runoff and spray drift concentrations in permanent water bodies (80 cm). The LOC was exceeded for the surface run-off scenario but not for spray drift (Table 16).

Estuarine / marine species: Acute toxicity studies with isofetamid were conducted with sheepshead minnow. The RQs were calculated using the same equations that were used for freshwater fish in a permanent water body (80-cm deep). Sheepshead minnow had acute RQs less than 1.

Aquatic Invertebrates

Freshwater invertebrates: Studies on *daphnids* (acute and chronic) were conducted with isofetamid; an acute study was also conducted with the Isofetamid 400SC. The risk quotients were calculated using one or the other of the following formulas: for an acute exposure: RQ = EEC in an 80-cm deep water body / (EC50 ÷ 2 or LC50 ÷ 2); for a chronic exposure: RQ = EEC in an 80-cm deep water body / NOEC. The acute risk quotients for *daphnids* exposed to isofetamid exceeded the LOC, however the chronic risk was not exceeded (Table 13). A Tier 1, refined chronic risk to daphnids was determined for runoff and spray drift concentrations in permanent water bodies (80 cm). The LOC was not exceeded in either case (Table 16).

Benthic dwelling aquatic invertebrates were not at acute risk of mortality as the screening level EEC for *Chironomus riparius* resulted in risk quotients below the LOC.

Estuarine / marine species: Acute toxicity studies with isofetamid were conducted with mysid shrimp, Eastern oyster and a marine diatom (*Skeletonema costatum*). The RQs were calculated using the same equations that were used for either freshwater invertebrates or algae in a permanent water body (80-cm deep). Mysids were the most sensitive taxa to isofetamid, the only marine species where the risk quotient exceeded the level of concern (Table 13). Mollusks and diatoms had acute RQs less than 1 (Table 13). A Tier 1, refined chronic risk to mysids was determined for runoff and spray drift concentrations in permanent water bodies (80 cm). The LOC was not exceeded in either case (Table 16).

Amphibians

No studies assessing the toxicity of isofetamid to amphibians were submitted. In order to determine risk to amphibians for exposure to isofetamid, the most sensitive acute and chronic endpoints for fish species were used as surrogate data along with the EEC in a 15-cm deep body of water. This water depth is representative of a seasonal water body used by amphibians to reproduce. More specifically, the risk quotients were calculated using the following formula: RQ = EEC in a 15-cm deep water body / most sensitive fish species LC_{50} /10 (from acute study), or NOEC (from chronic ELS study).

The risk from exposure of isofetamid to amphibians was determined using the acute LC50/10 for common carp (the lowest reported LC_{50} for fish), and the chronic NOEC from the fathead minnow ELS study. The resulting risk quotients (Table 13) indicate that isofetamid may pose an acute and chronic risk to amphibians in shallow waters. The endpoints from these studies were true endpoints as they were less than the highest concentration tested.

The risk to amphibians in shallow, non-permanent water bodies identified at the screening level was refined using spray drift and runoff inputs into a shallow (15 cm depth) water body (Table 16).

Aquatic Plants

Freshwater plants: Both freshwater algae and vascular plants were tested with isofetamid. The RQs were calculated using RQ = EEC in an 80-cm deep water body / (EC50 ÷ 2). Whenever more than one of the endpoints measured (cell density, total biomass, growth rate) was affected by the test substance, the most sensitive one was chosen for RQ calculations.

The risk quotient for duckweed indicates that the LOC was not exceeded for freshwater plants (Table 13). Risk quotients did not exceed the LOC for the most sensitive freshwater algal species tested (*Pseudokirchneriella subcapitata*).

Tier 1 Refinement – Aquatic Organisms

Risk to aquatic organisms was refined by characterizing EECs based on input from spray drift and overland runoff scenarios separately. Refined EECs for spray drift are expected to be 0.32 mg a.i./L in 80 cm water depth and 0.17 mg a.i./L in 15 cm depth (Table 16). Refined EECs from overland runoff sources represent the greatest potential for risk based on the proposed use pattern for 13-07G (Low growing Berries) and site characteristics for Atlantic Canada. Overlying water and porewater EECs in the table below were chosen to match the exposure time of the toxicity study as closely as possible (see Table 16 for Tier 1 risk quotients).

A Tier 1, refined acute and chronic risk to amphibians was determined for exposure to isofetamid from runoff and spray drift concentrations in shallow, non-permanent water bodies (15 cm). The LOC was exceeded for runoff but not for spray drift (Table 16).

A Tier 1, refined chronic risk to freshwater fish was determined for runoff and spray drift concentrations in permanent water bodies (80 cm). The LOC was exceeded for the runoff scenario but not for spray drift (Table 16).

Risk mitigation options for isofetamid are required. Buffer zones should provide protection from immediate adverse effects to in adjacent aquatic and terrestrial habitats due to off-site drift at the time of application. Surface runoff may occur at sufficient levels to introduce isofetamid into aquatic systems via soil particles although the resulting concentrations in the aquatic environment and, subsequently, sediment may be reduced via aquatic photolysis which is a major route of transformation. Benthic-dwelling aquatic invertebrates and vertebrates who are in close contact with sediments, where isofetamid will partition into, may be at chronic risk from elevated exposures. The PMRA does place a runoff-mitigation statement on all product labels, however this is a best management practices statement only and does not provide a quantifiable reduction in risk. Isofetamid residues are expected to partition to sediment where they will persist.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Control of botrytis bunch rot on grape

Results from nine field trials conducted in BC and the USA in 2010 – 2012 were reviewed. Botrytis bunch rot was recorded under moderate to high disease pressure (disease severity at 12 – 50% in non-treated control) in seven trials. Isofetamid 400SC Fungicide reduced bunch rot severity by 83% (52 – 100%) and 88% (77 – 100%) at 1.46 and 1.61 L/ha, respectively, compared to the non-treated control. The efficacy of Isofetamid 400SC Fungicide was

statistically comparable to Elevate 50WDG which is registered for control of bunch rot on grapes, and numerically superior to Pristine WG which is registered for suppression of the disease. All treatments of Isofetamid 400SC Fungicide, in five out of seven trials, achieved a level of disease control (severity) between 86% and 100%. The data supported a 14-day spray interval for control of botrytis bunch rot on grape. Control of botrytis bunch rot on grape is achievable with up to three applications of Isofetamid 400SC Fungicide per season when the other alternatives are available for the users. The claim for control of botrytis bunch rot on grape is supported.

5.1.2 Control of sclerotinia drop on lettuce (head and leaf)

Results from five field trials conducted in the USA in 2010 – 2012 were reviewed. Some trials were split into sub-trials based on the artificial inoculations of *Sclerotinia sclerotiorum* or *S. minor* and the lettuce cultivars tested. Sclerotinia drop caused by *S. minor* (in six trials) and by *S. sclerotiorum* (in three trials), were recorded with moderate to high disease pressure (disease severity at 16 – 48% and 11 – 37% in non-treated control, respectively). Isofetamid 400SC Fungicide at 0.9 L/ha reduced sclerotinia drop by 46% (29 – 64%) in the trials inoculated with *S. minor*, and by 37% (33 – 41%) in the trials inoculated with *S. sclerotiorum*, compared to the non-treated control. Endura 70DF (containing 70% boscalid, registered in the US), a product equivalent to Lance WDG registered in Canada, was applied in all trials as a commercial standard. The efficacy of Isofetamid 400SC was statistically comparable to Endura 70DF, which is justifiable to be used as a standard because no other product is available. Isofetamid 400SC Fungicide resulted in the greatest number and weight of total lettuce heads harvested in two out of the three trials, with an increase of lettuce heads by 41 – 105% and final yield by 53 – 72%. The data supported a 14-day spray interval for control of sclerotinia drop on lettuce. The demonstrated level of disease reduction was not ideal in the field trials; however, the level of disease control is considered acceptable to growers since the disease is very destructive and disease control has a high economic return. The claim for control of sclerotinia drop is supported.

5.1.3 Control of sclerotinia stem rot on rapeseed (Crop Subgroup 20A)

Results from six field trials on canola conducted in AB and MB in 2009 – 2012 were reviewed. Sclerotinia stem rot disease pressure was moderate to high with disease severity from 1.7 to 5.0 on a 0 – 5 disease rating scale in six trials. Isofetamid 400SC Fungicide reduced stem rot severity by 83% (64 – 91%) and 94% (91 – 97%) at the rates of 0.75 and 0.875 L/ha in four trials, respectively, compared to the non-treated control with two applications of Isofetamid 400SC. The efficacy of Isofetamid 400SC was statistically comparable to commercial standards applied in these trials. Canola yield was increased by 5% (1 – 13%) and 12% (1 – 18%) in the Isofetamid 400SC treatments at 0.75 and 0.875 L/ha in three trials, respectively. The results can be extrapolated from canola to all rapeseed crop subgroup (Crop Subgroup 20A) since canola is the representative crop for the crop subgroup and the causal pathogen is non-specific to host crops. The data supported a 14-day spray interval for control of sclerotinia stem rot on rapeseed. The claim for control of sclerotinia stem rot on rapeseed is supported.

5.1.4 Control of grey mold on low growing berry (Crop Subgroup 13-07G)

Results from five field trials on strawberry conducted in the USA in 2010 – 2012 were reviewed. Grey mold disease pressure was moderate to high with percent infected berries from 24 to 70% in two trials when disease assessment was made at harvest and from 11 to 83% in three trials when disease assessment was made after storage of the harvested berries. Isofetamid 400SC reduced grey mold by 76 – 84% at harvest or by 75 – 85% after the storage. The efficacy of Isofetamid 400SC Fungicide was comparable to the commercial standards Switch or Pristine applied in the same trials. The results can be extrapolated from strawberry to low growing berries crop subgroup (Crop Subgroup 13-07G) since strawberry is the representative crop for the crop subgroup and the causal pathogen is non-specific to host crops. The claim for control of grey mold on low growing berry is supported.

5.1.5 Control of dollar spot on turfgrass on golf courses and sod farms

Results from nine efficacy trials on creeping bentgrass conducted in the USA in 2010 – 2012 were reviewed. Dollar spot disease pressure was moderate with 23 – 102 infection centres per plot in five trials. Isofetamid 400SC Fungicide at 12.7 mL/100 m^2 significantly reduced dollar spot infection by 85% (57 – 100%) compared to the non-treated control in five trials. Isofetamid 400SC at 15.9 mL/100 m^2 significantly reduced the infection by 68% and 97% in two trials, which was numerically better than the 12.7 mL/100 m^2 rate applied in the same trials. The efficacy of Isofetamid 400SC Fungicide was comparable to the commercial standards Banner or Daconil applied in four trials.

Dollar spot disease pressure was high in four trials, with 195 – 336 infection centres per plot in two trials and 45 – 50% infected plants in the other two trials. Isofetamid 400SC Fungicide at 12.7 mL/100 m^2 significantly reduced dollar spot infection by 84% (52 – 100%) compared to the non-treated control in four trials. Isofetamid 400SC Fungicide at 15.9 mL/100 m^2 was applied in two trials, and the treatment significantly reduced the infection by 91% and 100% in these trials. The treatment at 15.9 mL/100 m^2 performed slightly better than the 12.7 mL/100 m^2 rate applied in the same trials. The efficacy of Isofetamid 400SC Fungicide was comparable to the commercial standards Banner or Daconil applied in all four trials. Isofetamid 400SC Fungicide demonstrated the efficacy for the control of dollar spot on turfgrass with the proposed use pattern. The claim for control of dollar spot on turfgrass is supported.

5.2 Phytotoxicity to Host Plants

No phytotoxicity or crop injury was reported.

5.3 Consideration of Benefits

5.3.2 Survey of Alternatives

Refer to Appendix I, Table 17 in Appendix I for a summary of the active ingredients currently registered for the same uses as Isofetamid 400SC Fungicide.

5.3.3 Compatibility with Current Management Practices Including Integrated Pest Management

Isofetamid 400SC Fungicide can be used in conjunction with current management practices, including IPM.

5.3.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Isofetamid 400SC Fungicide contains isofetamid, a Group 7 fungicide (Carboxamides). There is a medium to high risk for resistance development associated with the active ingredients because of its mode of action. The population of resistant isolates may increase in frequency when it is used repeatedly or exclusively. To maintain the performance of Isofetamid 400SC Fungicide in the field, appropriate resistance-management strategies should be implemented. Where possible, rotate Isofetamid 400SC Fungicide with fungicides having different mode of action that control the same pathogens and monitor fungal populations for resistance development.

5.4 Supported Uses

A summary of the proposed and accepted uses for Isofetamid 400SC Fungicide is presented in Table 18 in Appendix I.

6.0 Pest Control Product Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, Isofetamid was assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Isofetamid does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Table 6.2.1 for comparison with Track 1 criteria.
- Isofetamid does not form any transformation products that meet all Track 1 criteria.

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[5] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade Isofetamid does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.
- The end-use product, Isofetamid 400SC, does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.
- The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

Table 6.2.1 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria			
TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**		**Active Ingredient Endpoints**
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence:[3]	Soil	Half-life ≥ 182 days	Half-life = 66 days

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.

8 DIR2006-02, Formulants Policy and Implementation Guidance Document..

	Water	Half-life ≥ 182 days	Half-life = 40 days
	Sediment	Half-life ≥ 365 days	Half-life 175 days
	Air	Half-life ≥ 2 days or evidence of long range transport	1.4 hours
Bioaccumulation[4]	Log K_{ow} ≥ 5		2.5 (at pH 7)
	BCF ≥ 5000		not available
	BAF ≥ 5000		not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e. all other TSMP criteria are met).
[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for isofetamid is adequate to define the majority of toxic effects that may result from exposure to this compound. There were no treatment-related tumours in rats or mice. There was no evidence of immunotoxicity in mice. The battery of genotoxicity studies was negative. There were no concerns for neurotoxicity or reproductive toxicity. In short-term and chronic studies on laboratory animals, the primary targets were the liver and thyroid. There were no adverse fetal effects in the rabbit developmental toxicity study. In the rat developmental toxicity study, there were cardiovascular system malformations. This serious effect in the developing rat fetus occurred in the presence of equivocal maternal toxicity. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is isofetamid in plant products and in animal matrices. The proposed use of isofetamid on low growing berry (Crop Subgroup 13-07G), grapes, rapeseed (Crop

Subgroup 20A), lettuce and the importation of almond commodities do not constitute a risk of concern for chronic or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of isofetamid.

Commodity	Recommended MRL (ppm)
Leaf Lettuce	7
Head lettuce, raisins	5
Crop Subgroup 13-07G, Low growing berry	4
Crop Subgroup 13-07F, Small fruit vine climbing , except fuzzy kiwifruit	3
Canola oil, flaxseed oil, mustard seed oil, sesame oil	0.03
Crop Subgroup 20A, Rapeseed (Revised)	0.015
Almond Nuts	0.01*

* Proposed for import commodities.

Mixer/loaders and applicators handling Isofetamid 400SC Fungicide and workers entering treated areas are not expected to be exposed to levels of isofetamid that will result in risks of concern when Isofetamid 400SC Fungicide is used according to label directions. The personal protective equipment and restricted entry interval on the product label are adequate to protect workers.

Residential exposure to golfers entering treated golf courses is not expected to result in risks of concern when Isofetamid 400SC Fungicide is used according to label directions.

Additionally, no risks of concern were identified for the general public entering treated areas at PYO operations.

7.2 Environmental Risk

Isofetamid, formulated as Isofetamid 400SC Fungicide, is intended for use as a broad spectrum systemic fungicide as a post-emergent foliar spray on grapes, lettuce, rapeseed, Crop Group 13-07G (Low growing Berries) and turf. The primary exposure pathways are expected to be via terrestrial plants and soil (aerobic and anaerobic soil), riparian wetland foliage and soil and aquatic sediments.

Effects of isofetamid on terrestrial organisms were based upon evaluation of toxicity data for one mammal and three bird species representing vertebrates (acute gavage, short- and long-term dietary exposure); one bee species, two other arthropod species and one earthworm species representing invertebrates (acute or short-term exposure); and ten crop species representing plants (short-term exposure). Effects of isofetamid on aquatic organisms were based upon evaluation of toxicity data for fourteen species. Effects on marine aquatic organisms were based on review of studies for four saltwater species representing marine invertebrates, marine algae and marine fish. Effects on freshwater aquatic species were based on review of three freshwater

algae species (short term), one aquatic plant species (short term), four freshwater fish species (short and long term) and two freshwater aquatic invertebrate species (short and long term). Toxicity of the major transformation products of isofetamid, PPA and IBA were not provided.

Earthworms, honeybees, predators and parasites, birds, small mammals and terrestrial plants may be exposed to isofetamid residues in the environment through direct contact with spray droplets during foliar application, contact with treated materials (plants, soil) or from ingestion of contaminated food. Where applicable, the assessment was based on the assumption that the diet consists entirely of food sources contaminated with isofetamid. In addition, it was also assumed that non-target plants and avian and mammalian food sources outside of treated crops were at least 1 m downwind from the last spray swath and would therefore only be exposed to 6% of the expected on-field concentrations through spray drift from field-sprayer applications ($EEC_{off\text{-}field} = EEC_{in\text{-}field} \times 0.06$).

Screening-level risk quotients determined birds feeding on treated fields exceeded the level of concern for all sizes of birds on a reproductive basis. Further characterization of risk using mean residues showed reproductive risk to all feeding guilds of small birds, medium sized birds that consume only insects and fruit and large birds that feed exclusively on vegetation. There was no risk to birds feeding in areas off treated fields. Considering that these food items are relevant for turf (sod farms and golf courses), further refinement was not attempted as there is a clear risk when considering both the maximum residues and the mean residues which means that adverse effects are likely to occur at a broad range of residue concentrations on food in the field. An appropriate label statement to mitigate risk was added to the Isofetamid 400SC Fungicide label.

The level of concern (LOC) was not exceeded following acute exposure of isofetamid to small, wild mammals although screening level risk quotients calculated based on reproductive endpoints for medium sized mammals consuming grass exclusively exceeded the level of concern. Therefore, small, wild herbivorous mammals of medium size (35 g) feeding only on short grass could be at risk from isofetamid for on-field exposure. Reproductive risks are not expected in mammals foraging exclusively off-field. A refinement conducted considering mean residues found no exceedances of the LOC for either on, or off-field scenarios for medium sized mammals feeding exclusively on grass. It is expected that mammals will be exposed to a range of concentrations on food but effects are only expected to occur at the highest end of the residue concentration spectrum. Further refinements were not required.

No risk was found for earthworms or bees. Based on mortality observed in *T. pyri*, isofetamid may pose a risk to predatory arthropods in treated fields but not on areas adjacent to fields. Mitigation measures are therefore not required. Risk quotients did not indicate risk to terrestrial plants for seedling emergence or vegetative vigour at the highest cumulative application rate.

Isofetamid is not expected to bioconcentrate or bioaccumulate in aquatic organisms. In the freshwater environment, isofetamid has no risk of acute effects to invertebrates, benthic invertebrates, algae or vascular plants. Isofetamid exhibited acute toxic effects to fish on an acute and chronic basis and to aquatic invertebrates on a chronic basis. In the marine environment, isofetamid poses an acute risk to fish, aquatic invertebrates, mollusks and algae.

To assess the risk to amphibians for acute and chronic exposure, the toxicity values for the most sensitive fish species were used as surrogate data along with the expected environmental concentration in a 15 cm deep body of water. The screening level risk quotients exceeded the level of concern for amphibians on an acute and chronic basis. Risk mitigation options for amphibians exposed to isofetamid are limited. Buffer zones can provide protection from adverse effects in adjacent aquatic habitats due to off-site drift at the time of application. However, environmental concentrations in water are expected to be higher due to runoff from treated fields than from spray drift inputs. Amphibians are expected to be at short term (acute) and chronic risk from elevated exposures. The PMRA does place a runoff-mitigation statement on all product labels, however this is a best management practices statement only and does not provide a quantifiable reduction in risk. Therefore, there are no effective mitigation measures available to allow the PMRA to mitigate the risk from runoff. Due to isofetamid's persistence in sediments, annual application is expected to lead to continued accumulation in adjacent aquatic sediments through both spray drift and runoff inputs.

7.3 Value

Value information was provided to support the use of Isofetamid 400SC Fungicide to control various *Botrytis* and *Sclerotinia* diseases on grape, lettuce (head and leaf), rapeseed (Crop Subgroup 20A), low growing berry (Crop Subgroup 13-07G), and turfgrass on golf courses and sod farm. The registration of Isofetamid 400SC Fungicide offers an additional product for Canadian growers to manage these diseases.

8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Technical Isofetamid Fungicide and Isofetamid 400SC Fungicide, containing the technical grade active ingredient isofetamid, to control various *Botrytis* and *Sclerotinia* diseases on grape, lettuce (head and leaf), rapeseed, low growing berry and turfgrass on golf courses and sod farms.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
μm	micrometer
1/n	exponent for the Freundlich isotherm
♂	male
♀	female
abs	absolute
AD	administered dose
ADI	acceptable daily intake
AHETF	Agricultural Handlers Exposure Task Force
a.i.	active ingredient
ALP	alkaline phosphatase
ALS	acetolactate synthase
ALT	alanine transferase
APTT	activated partial thromboplastin time
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate transferase
atm	atmosphere
ATPD	area treated per day
AUC	area under the curve
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
cm	centimetres
C_{max}	maximum concentration
DF	dry flowable
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DF	dry flowable
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the dose required to observe a 75% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
dw	dry weight
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EEC	estimated environmental concentration
EPA	Environmental Protection Agency
ER_{25}	effective rate for 25% of the population
F_0	initial parental generation

F_1	first generation
F_2	second generation
fc	food consumption
FOB	functional observational battery
FRAC	Fungicide Resistance Action Committee
g	gram
GD	gestation day
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practices
ha	hectare(s)
HAFT	highest average field trial
HDPE	high-density polyethylene
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
hr	hour
ILV	independent laboratory validation
IPM	integrated pest management
IUPAC	International Union of Pure and Applied Chemistry
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
kg	kilogram
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
MAS	maximum average score
mg	milligram
mL	millilitre
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
NAFTA	North American Free Trade Agreement
NC	not classified
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required

NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
ORETF	Outdoor Residential Exposure Task Force
PBI	plantback interval
PET	polyethylene terephthalate
PFC	plaque forming cell
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	post-natal day
ppm	parts per million
RAC	raw agricultural commodity
RD	residue definition
RSD	relative standard deviation
SC	soluble concentrate
SDH	Succinate dehydrogenase
SDHI	Succinate dehydrogenase inhibitor
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
PPE	personal protective equipment
PYO	pick-your-own
REI	restricted-entry interval
rel	relative
SOP	standard operating procedure
STMdR	supervised trial median residue
TC	transfer coefficient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TTR	transferable turf residue
UAN	urea ammonium nitrate
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
WDG	Water dispersible granule
WG	Wettable granule
wt	weight

Appendix I Tables and Figures

NOTE: IKF5411 = Isofetamid

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Soil	n/a	Parent	HPLC-MS/MS	0.01 mg/kg		2273877, 2273876
		4HP				
Sediment		Parent				2273878
		4HP				
Surface water		Parent		0.05 µg/L		2273879
		3-MTCAM				
		IBA				
		PPA				
Drinking water		Parent				
		3-MTCAM				
		IBA				
		PPA				
Plant	JSM0119	Isofetamid and GPTC	LC-MS/MS	0.01	Grape, lettuce, rape seed, almond and dry bean	PMRA #s 2273761, 2273762, 2273763
Animal	SMV 8256542-04V and SMV 8256542-03V	Isofetamid, 4HP, PPA, and 5-HPPA	LC-MS/MS	0.01	Milk, muscle, fat, kidney, liver and eggs	PMRA # 2327358

Table 2 Toxicity Profile of Isofetamid 400SC

Study Type/ Animal/ PMRA #	Study Results
Acute Toxicity Studies – Isofetamid 400SC Fungicide	
Acute Oral Toxicity (gavage) Sprague-Dawley rats PMRA 2273735	LD_{50} > 2000 mg/kg bw **Low toxicity**
Acute Dermal Toxicity Sprague-Dawley rats PMRA 2273736	LD_{50} > 2000 mg/kg bw **Low toxicity**
Acute Inhalation Toxicity	LC_{50} > 5.13 mg/L **Low toxicity**

Study Type/ Animal/ PMRA #	Study Results
Sprague-Dawley rats PMRA 2273737	
Eye Irritation NZW rabbits PMRA 2273738	MAS = 0/110 for unwashed eyes **Non-irritating**
Dermal Irritation NZW rabbits PMRA 2273839	MAS = 0/8 **Non-irritating**
Skin Sensitization, LLNA CBA/J mice PMRA 2273740	SI = 1.7, 1.6, 2.1 **Not a potential skin sensitizer**

Table 3 Toxicity Profile of Technical Isofetamid

(Effects are known or assumed to occur in both sexes unless otherwise noted; sex specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.)

Study Type/ Animal/ PMRA #	Study Results
Toxicokinetic Studies	
Metabolism and pharmacokinetics, gavage, PMRA 2273873 98.9% pure, radiolabeled on benzene ring or the 2 carbon of the thiophene ring 4-18 Wistar rats/sex/group, low dose = 5 mg/kg bw, high dose = 200 mg/kg bw There was > 89% recovery of the radiolabel for all studies with little difference in the rate or route of excretion between the two radiolabeled compounds. The biliary study showed rapid absorption with the low dose being ~93% absorbed, the radiolabel being rapidly eliminated in the bile and urine. The single and repeat dose studies showed a sex-related difference. Male rats, regardless of dose, eliminated most of the radiolabel in the feces (71-95% ♂, 37-82% ♀) while female rats eliminated approximately five-times more radiolabel in the urine (3-13% ♂, 10-50% ♀). Elimination for both sexes was rapid, with the majority of the radiolabel recovered within 48 hours of treatment. Little to no radiolabel was recovered in the expired air. As the biliary studies indicated, biliary excretion was the major route of elimination for both sexes and suggested reabsorption of biliary metabolites with subsequent excretion in urine. Distribution studies indicated that the radiolabel did not accumulate in any of the tissues. All studies showed there was no effect in the disposition of the radiolabel relative to its position on the compound. There were no significant differences in the pharmacokinetics of IKF-5411 between the radiolabeled forms of the test material; however, test material exposure was approximately two-fold greater in males. Maximum plasma concentrations were achieved between 2 and 6 hours at the low-dose and ~8 hours at the high dose. The plasma elimination half-lives were ~38 hours regardless of sex, dose, or radiolabel position. The toxicokinetics of IKF-5411 were not linear relative to dose; a 40-fold increase in dose resulted in a ~25-fold increase in C_{max} and AUC. This suggests that routes of absorption were saturated at the high-dose. The blood:plasma ratio increased at later time intervals suggesting an association of IKF-5411, or its radiolabeled metabolites, with the cellular fraction of the	

Study Type/ Animal/ PMRA #	Study Results
blood. IKF-5411 underwent extensive metabolism following oral administration with no qualitative sex or radiolabel differences in metabolism. The test material was rapidly metabolized by three main routes; O-dealkylation, hydroxylation, and subsequent glucuronidation. Minor routes included methylation, sulfation and cleavage between the benzene and thiophene-ring.	
Acute Toxicity Studies – Technical	
Acute Oral Toxicity (gavage) Sprague-Dawley rats PMRA 2273826	LD_{50} > 2000 mg/kg bw **Low toxicity**
Acute Dermal Toxicity Sprague-Dawley rats PMRA 2273827	LD_{50} > 2000 mg/kg bw **Low toxicity**
Acute Inhalation Toxicity Sprague-Dawley rats PMRA 2273828	LC_{50} > 4.82 mg/L **Low toxicity**
Eye Irritation NZW rabbits PMRA 2273829	MAS = 0.2/110 for unwashed eyes **Minimally irritating**
Dermal Irritation NZW rabbits PMRA 2273830	MAS = 0/8 **Non-irritating**
Skin Sensitization, LLNA CBA/J mice PMRA 2273831	SI = 1.0, 1.1, 1.1 **Not a potential skin sensitizer**
Short-Term Toxicity Studies	
28-Day Dermal Toxicity Sprague-Dawley rats PMRA 2273846	NOAEL 1000 mg/kg bw/day
90-Day Oral Toxicity (diet) CD-1 mice PMRA 2273837	NOAEL 129/161 mg/kg bw/day **≥ 129 mg/kg bw/day:** (effects considered marginal/adaptive or non-adverse at this dose level) ↑ glucose, phosphorus, albumin/globulin ratio ♂; ↓ albumin/globulin ratio ♀ **1067 mg/kg bw/day:** ↑ liver wt, enlarged liver, hepatocellular hypertrophy; ↓ bwg, ↑ ALT, urea, ↓ potassium, ↑ adrenal wt, cortical hypertrophy of adrenals ♀

Study Type/ Animal/ PMRA #	Study Results
28-Day Oral Toxicity (diet) Brl-WIST rats PMRA 2273843	Supplemental, range-finding **≥ 210 mg/kg bw/day:** ↑ rel liver wt, ↓ total bilirubin **1271 mg/kg bw/day:** ↑ abs liver wt, ↑ dark liver, ↑ GGT; ↑ creatinine ♂; ↓ spleen wt, ↑ total protein ♀ No histopathology conducted
90-Day Oral Toxicity (diet) with FOB Brl-WIST rats PMRA 2273836	NOAEL 6.65/7.83 mg/kg bw/day **≥ 68.9 mg/kg bw/day:** ↑ GGT, ↑ rel liver wt, ↑ hepatocellular hypertrophy; ↑ thyroid follicular cell hypertrophy ♂; ↑ APTT, ↓ ALT, ↑ adrenal wt ♀ **637 mg/kg bw/day:** ↑ total protein, globulin, cholesterol, ↑ abs liver wt, ↑ dark liver; ↑ APTT, ↑ prothrombin time, ↑ ALT ♂; ↓ ALP, AST, ↑ triglycerides, ↑ thyroid follicular cell hypertrophy, ↑ adrenal hypertrophy ♀ No FOB or motor activity effects
28-Day Oral Toxicity (diet) Beagle dogs PMRA 2273843	Supplemental **≥ 30.3 mg/kg bw/day:** ↑ liver wt **≥ 89.8 mg/kg bw/day:** ↑ ALP, triglycerides, ↑ enlarged livers, centrilobular hepatocellular hypertrophy
90-Day Oral Toxicity (diet) Beagle dogs PMRA 2273839	NOAEL 29.3/32.7 mg/kg bw/day **≥ 29.3 mg/kg bw/day:** (effects considered adaptive or non-adverse at this dose level) ↓ albumin; ↑ liver wt, ↑ ALP, GGT, ↑ enlarged liver, centrilobular hepatocellular hypertrophy ♀ **301 mg/kg bw/day:** ↑ thyroid follicular cell hypertrophy, ↑ triglycerides; ↓ bwg, ↑ enlarged liver, ↑ centrilobular hepatocellular hypertrophy, ↑ zona fasciculata cell hypertrophy in adrenals ♂
1-Year Toxicity (diet) Beagle dogs PMRA 2273842	NOAEL 5.34/5.58 mg/kg bw/day **166 mg/kg bw/day:** ↑ liver wt, enlarged liver, ↑ centrilobular hepatocellular hypertrophy, ↑ ALP, triglycerides, ↓ albumin; ↑ GGT, cholesterol ♂; ↑ darkened liver ♀
Chronic Toxicity/Oncogenicity Studies	
1.5-Year Oncogenicity (diet) CD-1 mice PMRA 2273848	NOAEL 92/118 mg/kg bw/day **≥ 92 mg/kg bw/day:** borderline ↓ bw (3% ♂; 6% ♀), bwg (10% ♂; 11% ♀) **431 mg/kg bw/day:** ↑ liver wt; ↑ adrenal wt ♂ No evidence of oncogenicity
1-Year Oral Toxicity (diet) with FOB Brl-WIST rats PMRA 2273847	NOAEL 22.7/30.0 mg/kg bw/day **237 mg/kg bw/day:** ↑ APTT, hemoglobin distr. width, ↑ GGT, cholesterol, ↓ bilirubin, ↑ liver wt, thyroid wt, ↑ hepatocellular hypertrophy, tubular basophilic change in kidneys, thyroid follicular cell hypertrophy; ↑ prothrombin time, ↑ calcium, ↑ fatty change, hepatocellular eosinophilic inclusion bodies ♂; ↓ hemoglobin, ↑ globulins, ↓ creatinine ♀ No FOB or motor activity effects
2-Year Oncogenicity (diet) Brl-WIST rats	NOAEL 20.3/26.1 mg/kg bw/day **≥ 20.3 mg/kg bw/day:** ↑ abs liver wt ♂ **210 mg/kg bw/day:** ↓ bwg 2nd year only, ↑ rel liver wt, ↑ thyroid follicular cell

Study Type/ Animal/ PMRA #	Study Results
PMRA 2273850	hypertrophy, thyroid follicular cyst; ↑ hepatocyte hypertrophy and hepatocellular eosinophilic inclusion bodies; ↑ abs liver wt, dark liver, hepatocellular brown pigment (lipofuscin) deposition ♀ No evidence of oncogenicity
Developmental/Reproductive Toxicity Studies	
One-Generation Reproductive Toxicity (diet) Sprague-Dawley rats PMRA 2273854	Supplemental, range-finding Parental toxicity **≥ 609 mg/kg bw/day:** ↑ liver wt, hepatocellular hypertrophy, thyroid follicular cell hypertrophy **903 mg/kg bw/day:** ↑ bwg (lactation days 0-21), thyroid wt ♀ Reproductive toxicity No effects Offspring toxicity **≥ 609 mg/kg bw/day:** ↓ bw (PND 21) ♀ **903 mg/kg bw/day:** ↓ bw (PND 21) ♂
Two-Generation Reproductive Toxicity (diet) Sprague-Dawley rats PMRA 2273857	Parental toxicity NOAEL 65.8 mg/kg bw/day **≥ 65.8 mg/kg bw/day:** ↑ liver wt ♀ F_0F_1 **679 mg/kg bw/day:** ↑ thyroid wt, ↑ hepatocellular hypertrophy, thyroid follicular cell hypertrophy; ↑ liver wt, ↑ liver cytoplasmic eosinophilic inclusion bodies F_1, ↓ spleen wt F_1 ♂; ↑ bwg during lactation only♀ Reproductive toxicity NOAEL 679 mg/kg bw/day Offspring toxicity NOAEL 65.8 mg/kg bw/day **679 mg/kg bw/day:** ↓ bw (~10%), bwg (~20% mostly PND14-21), ↓ abs spleen wt, ↓ abs thymus wt; ↑ time to vaginal patency (1.7 days), likely 2° to bw F_1 ♀ No evidence of sensitivity of the young
Developmental Toxicity (gavage) Sprague Dawley rats PMRA 2273863	Supplemental, range-finding Maternal toxicity **≥ 300 mg/kg bw/day:** salivation, chin rubbing, ↑ liver wt, all effects considered non-adverse Developmental toxicity No adverse effects noted
Developmental Toxicity (gavage) Sprague Dawley rats PMRA 2273865	Maternal toxicity NOAEL 100 mg/kg bw/day **≥ 300 mg/kg bw/day:** salivation, chin rubbing, ↑ adjusted and relative liver wt Developmental toxicity NOAEL 100 mg/kg bw/day **≥ 300 mg/kg bw/day:** visceral malformations in the heart and/or major blood vessels including malrotated heart, narrow pulmonary trunk, dorsally displaced pulmonary trunk, muscular ventricular septal defect, membranous ventricular septal defect*, absent ductus arteriosus, ascending aorta/pulmonary trunk fistula* and incomplete caudal vena cava

Study Type/ Animal/ PMRA #	Study Results
	with persistent cardinal vein* * = zero incidence in historical controls fetuses (litters) with visceral malformations = 0(0), 0(0), 1(1), 2(2) **1000 mg/kg bw/day:** left-sided umbilical artery variation No evidence of sensitivity of the young; malformations at a maternally toxic dose
Developmental Toxicity (gavage) Japanese White rabbits PMRA 2273866	Supplemental, range-finding Maternal toxicity No treatment-related effects Developmental toxicity No treatment-related effects
Developmental Toxicity (gavage) Japanese White rabbits PMRA 2273867	Maternal toxicity NOAEL 300 mg/kg bw/day **1000 mg/kg bw/day:** ↑ liver wt Developmental toxicity NOAEL 1000 mg/kg bw/day No evidence of sensitivity of the young or malformations
Genotoxicity Studies	
Bacterial Gene Mutation Assay (in vitro) Salmonella/Escherichia TA98, TA100, TA1535, TA1537, WP2 uvrA PMRA 2273868	Negative
Mammalian Gene Mutation Assay (in vitro) Mouse lymphoma L5178Y cells PMRA 2273869	Negative
Mammalian Chromosome Aberration Assay (in vitro) Chinese hamster lung cells PMRA 2273870	Negative
Mammalian Micronucleus Assay (in vivo) ICR mice	Negative

Study Type/ Animal/ PMRA #	Study Results
PMRA 2273872	
Neurotoxicity Studies	
Acute Neurotoxicity (gavage) Sprague-Dawley rats PMRA 2273859	NOAEL 1000 mg/kg bw **2000 mg/kg bw:** ↓ ambulatory motor activity ♀
90-Day Neurotoxicity (diet) Sprague-Dawley rats PMRA 2273861	NOAEL 1049 mg/kg bw/day **1049 mg/kg bw/day:** borderline and sporadic ↓ bwg ♂, not considered adverse
Immunotoxicity Studies	
Immunotoxicity (diet) Plaque forming cell assay CD-1 mice PMRA 2273852	NOAEL = 644 mg/kg bw/day **1380 mg/kg bw/day:** ↑ liver size No evidence of decreased spleen cells, specific activity (PFC/10^6 spleen cells) or total activity (PFC/spleen) No evidence of immunotoxicity

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Isofetamid

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or MOE
Acute dietary females 13-49 years of age	Rat oral (gavage) developmental toxicity	NOAEL = 100 mg/kg bw/day Cardiovascular malformations	300
	ARfD (females 13-49 years of age) = 0.3 mg/kg bw		
Acute dietary general population excluding ♀ 13-49 years of age	Not required		
Repeated dietary	Dog 1-year oral toxicity	NOAEL = 5.3 mg/kg bw/day Liver toxicity	100
	ADI = 0.05 mg/kg bw/day		
Short and Intermediate-term dermal[2] (adult)	Rat oral (gavage) developmental toxicity	NOAEL 100 mg/kg bw/day Cardiovascular malformations	300
Short and Intermediate-term inhalation[3] (adult)	Rat oral (gavage) developmental toxicity	NOAEL 100 mg/kg bw/day Cardiovascular malformations	300
Aggregation of Short- and Intermediate-term oral, dermal and inhalation exposure (adult)	Rat oral (gavage) developmental toxicity	NOAEL 100 mg/kg bw/day Cardiovascular malformations	300
Short- and Intermediate-term dermal[2] (youths 6-11 years of age	Rat 28-day dermal toxicity	NOAEL 1000 mg/kg bw/day No effects	100
Short- and Intermediate-term inhalation[3] (youths 6-11 years of age)	Rat 90-day oral toxicity	NOAEL 7 mg/kg bw/day Liver toxicity	100

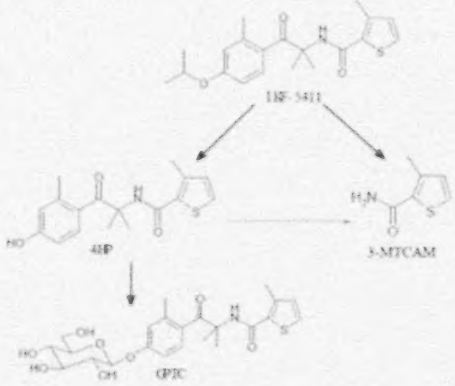
Aggregation of Short- and Intermediate-term oral and inhalation exposure (youths 6-11 years of age)	Rat 90-day oral toxicity	NOAEL 7 mg/kg bw/day Liver toxicity	100
Cancer	Not required		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary and residential risk assessment; MOE refers to the target margin of exposure for occupational assessment
[2] The dermal absorption value for exposure assessments was 13%
[3] For inhalation exposure assessments, 100% absorption was assumed

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN GRAPE			**PMRA # 2273758**	
Radiolabel Position	[^{14}C-benzene] and [^{14}C-thiophene]			
Test Site	In greenhouse			
Treatment	Foliar treatment			
Total Rate	3× 750-753 g a.i./ha; total rate of 2250-2260 g a.i./ha			
Formulation	Suspension concentrate (SC) formulation			
Preharvest interval	14 days			
Matrices	**PHI (days)**	**[^{14}C-benzene] TRRs (ppm)**	**[^{14}C-thiophene] TRRs (ppm)**	
Grape foliage	14	16.93	15.96	
Grape fruit	14	0.729	0.644	
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[^{14}C-benzene]**	**[^{14}C-thiophene]**	**[^{14}C-benzene]**	**[^{14}C-thiophene]**
Grape foliage	Isofetamid	Isofetamid	GPTC	3-MTCAM, GPTC
Grape fruit	Isofetamid, GPTC	Isofetamid	-	3-MTCAM, GPTC

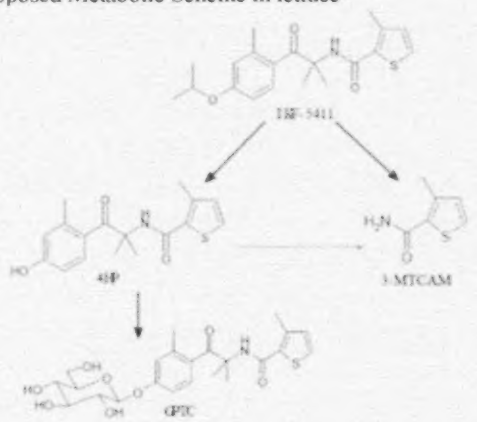
Proposed Metabolic Scheme in grape



NATURE OF THE RESIDUE IN LETTUCE	PMRA # 2273759
Radiolabel Position	[14C-benzene] and [14C-thiophene]
Test Site	In greenhouse
Treatment	Foliar treatment
Total Rate	3× 753-757 g a.i./ha; total rate of 2260--2310 g a.i./ha

Formulation	Suspension concentrate (SC) formulation			
Preharvest interval	14 days			
Matrices	PHI (days)	[14C-benzene] TRRs (ppm)	[14C-thiophene] TRRs (ppm)	
Lettuce wrappers	18	2.56	1.69	
Lettuce heads	18	0.065	0.090	
Metabolites Identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[14C-benzene]	[14C-thiophene]	[14C-benzene]	[14C-thiophene]
Lettuce wrappers	Isofetamid	Isofetamid	GPTC, 4HP	4HP, 3-MTCAM, GPTC
Lettuce heads	Isofetamid, GPTC	Isofetamid	4HP	4HP, 3-MTCAM, GPTC

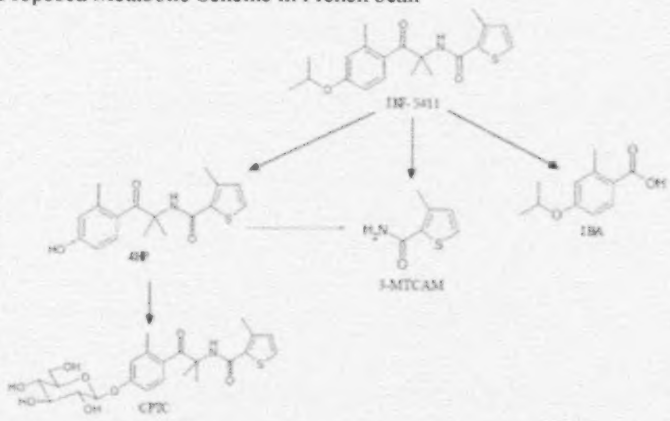
Proposed Metabolic Scheme in lettuce



NATURE OF THE RESIDUE IN FRENCH BEAN	PMRA # 2273760			
Radiolabel Position	[14C-benzene] and [14C-thiophene]			
Test Site	In greenhouse			
Treatment	Foliar treatment			
Total Rate	3× 750 g a.i./ha; total rate of 2250 g a.i./ha			
Formulation	Suspension concentrate (SC) formulation			
Preharvest interval	0, 14 and 68 days			
Matrices	PHI (days)	[14C-benzene] TRRs (ppm)	[14C-thiophene] TRRs (ppm)	
Whole plant (1st harvest)	0	22.34	25.46	
Forage (2nd harvest)	14	10.54	11.60	
Pod (2nd harvest)	14	0.261	0.413	
Immature seeds (2nd harvest)	14	0.143	0.403	
Straw (3rd harvest)	68	3.267	4.944	
Pod (3rd harvest)	68	0.212	0.372	
Mature seeds (3rd harvest)	68	0.028	0.060	
Metabolites Identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[14C-benzene]	[14C-thiophene]	[14C-benzene]	[14C-thiophene]
Whole plant (1st harvest)	Isofetamid	Isofetamid	IBA	4HP, 3-MTCAM

Forage (2nd harvest)	Isofetamid	Isofetamid	IBA, GPTC	4HP, 3-MTCAM, 3-MTCA, GPTC
Pod (2nd harvest)	Isofetamid	Isofetamid	GPTC	3-MTCAM, GPTC
Immature seeds (2nd harvest)	Isofetamid	Isofetamid	-	3-MTCAM
Straw (3rd harvest)	Isofetamid	Isofetamid	GPTC	4HP, 3-MTCAM, GPTC
Pod (3rd harvest)	Isofetamid	Isofetamid	-	-
Mature seeds (3rd harvest)	-	-	Isofetamid	Isofetamid

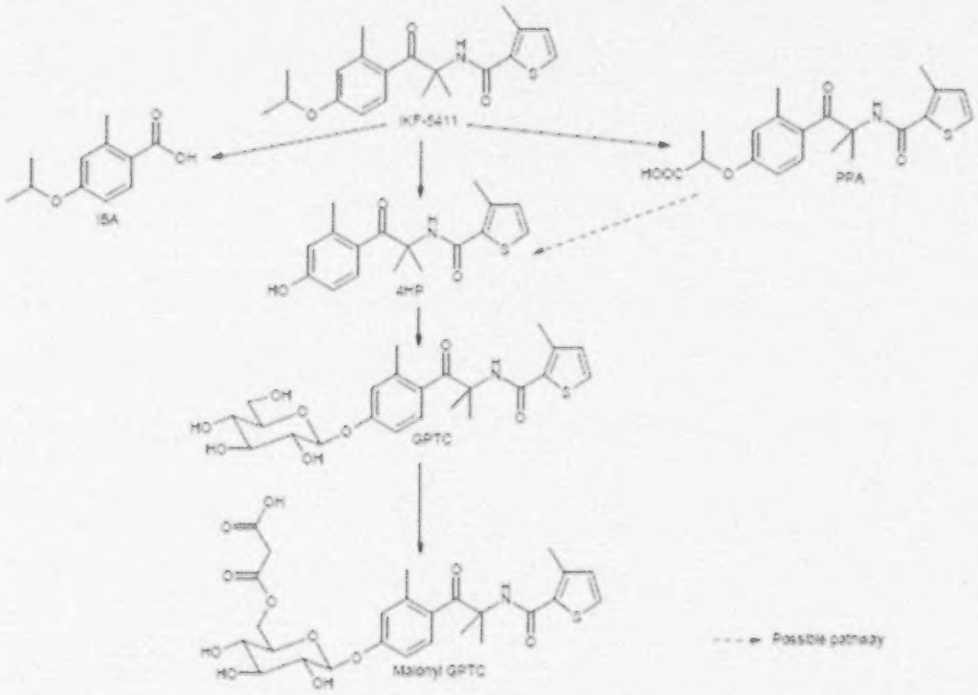
Proposed Metabolic Scheme in French bean



CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, carrot and wheat				PMRA #s 2273772 and 2273773	
Radiolabel Position		[14C-benzene] and [14C-thiophene]			
Test site		In greenhouse			
Formulation		Suspension			
Application rate and timing		Bare soil was treated at 2250 g a.i./ha, and aged for 30, 120 and 365 days.			
Metabolites Identified		Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Matrices	PBI (days)	[14C-benzene]	[14C-thiophene]	[14C-benzene]	[14C-thiophene]
Lettuce	30	GPTC, malonyl-GPTC	GPTC, malonyl-GPTC	Isofetamid, IBA, 4HP	Isofetamid, PPA, 4HP
	120	GPTC, malonyl-GPTC	GPTC	Isofetamid, PPA, 4HP	4HP, malonyl-GPTC
	365	GPTC, malonyl-GPTC	-	Isofetamid	-
Carrot (foliage)	30	-	GPTC, malonyl-GPTC	Isofetamid, IBA, PPA, 4HP, GPTC, malonyl-GPTC	Isofetamid, PPA, 4HP
	120	Isofetamid	Isofetamid	PPA, 4HP,GPTC, malonyl-GPTC	4HP, malonyl-GPTC
	365	-	Malonyl-GPTC	Isofetamid, 4HP, GPTC, malonyl-GPTC	Isofetamid, PPA, GPTC
Carrot (root)	30	Isofetamid, malonyl-GPTC	GPTC, malonyl-GPTC	PPA, 4HP, GPTC	Isofetamid, PPA
	120	Isofetamid, malonyl-GPTC	Isofetamid, malonyl-GPTC	PPA, 4HP, GPTC	PPA, GPTC
	365	Isofetamid, malonyl-GPTC	Isofetamid	-	Malonyl-GPTC

Wheat forage	30	Malonyl-GPTC	Malonyl-GPTC	Isofetamid, PPA, IBA, 4HP, GPTC	Isofetamid, PPA, 4HP, GPTC
	120	Malonyl-GPTC	Malonyl-GPTC, GPTC	Isofetamid, PPA, 4HP, GPTC	Isofetamid, PPA, 4HP
	365	GPTC, malonyl-GPTC	Malonyl-GPTC	Isofetamid, 4HP	Isofetamid, 4HP
Wheat hay	30	Malonyl-GPTC	Isofetamid, malonyl-GPTC	Isofetamid, PPA, IBA, 4HP, GPTC	PPA, 4HP, GPTC
	120	Malonyl-GPTC	Malonyl-GPTC	Isofetamid, PPA, 4HP, GPTC	Isofetamid, PPA, 4HP, GPTC
	365	Malonyl-GPTC	Malonyl-GPTC	Isofetamid, PPA, GPTC	Isofetamid, GPTC
Wheat straw	30	Malonyl-GPTC	PPA, malonyl-GPTC	Isofetamid, PPA, IBA, 4HP, GPTC	Isofetamid, 4HP, GPTC
	120	4HP	-	Isofetamid, PPA, GPTC, malonyl-GPTC	Isofetamid, 4HP, PPA, malonyl-GPTC, GPTC
	365	Malonyl-GPTC	Malonyl-GPTC	Isofetamid, PPA, 4HP, GPTC	4HP, PPA, GPTC
Wheat grain	30	-	-	PPA, malonyl-GPTC	PPA, malonyl-GPTC
	120	-	-	-	-
	365	-	-	PPA	-

Proposed Metabolic Scheme in rotational crops



NATURE OF THE RESIDUE IN LAYING HEN	PMRA #s 2273753 and 2273753

Ten laying hens were dosed orally with [14C-isofetamid] at 10 ppm in feed by gelatin capsule once daily for 14 days. Samples of excreta were collected daily. Samples of eggs were collected twice daily. The hens were euthanized 23 hours after administration of the final dose.

Matrices	[14C-benzene]		[14C-thiophene]	
	TRRs (ppm)	% of Administered Dose*	TRRs (ppm)	% of Administered Dose*
Excreta	-	115.5 (98.6)	-	103.1 (98.8)
Cage wash	-	1.329 (1.1)	-	1.090 (1.0)
Egg yolk	0.215	0.158 (0.13)	0.183	0.120 (0.12)
Egg white	0.003344	0.008 (0.007)	0.004798	0.009 (0.009)
Muscle (breast)	0.009655	0.004 (0.003)	0.009342	0.003 (0.003)
Muscle (thigh)	0.01532	0.002 (0.002)	0.01374	0.001 (0.001)
Fat (peritoneal)	0.01435	0.002 (0.002)	0.009207	0.002 (0.002)
Fat (perirenal)	0.05121	<0.001 (<0.001)	0.02681	<0.001 (<0.001)
Skin (including subcutaneous fat)	0.03490	0.002 (0.002)	0.03014	0.001 (0.001)
Liver	0.2071	0.041 (0.04)	0.1802	0.038 (0.04)

* Values in parentheses represent the percentage harmonized based on the total AD from all samples.

Metabolites identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[14C-benzene]	[14C-thiophene]	[14C-benzene]	[14C-thiophene]
Egg Yolk	-	-	Isofetamid, 4HP, PPA, IBA	Isofetamid, 4HP, PPA, 3-MTCAM
Liver	-	-	Isofetamid, 4HP, PPA, IBA	4HP, PPA
Muscle	-	-	4HP	-
Fat	-	-	Isofetamid, 4HP	Isofetamid, 4HP
Skin	-	-	PPA	4HP

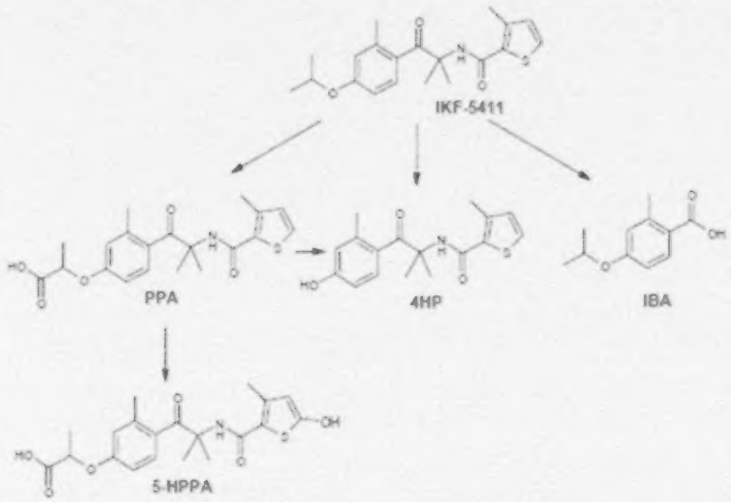
NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA #s 2273754 and 2273757

Two lactating goats were dosed orally with [14C-isofetamid] at 10 ppm in feed by gelatin capsule once daily for 7 days. Samples of excreta were collected daily and milk was collected twice daily. The goats were euthanized 23 hours after administration of the final dose.

Matrices	[14C-benzene]		[14C-thiophene]	
	TRRs (ppm)	% of Administered Dose	TRRs (ppm)	% of Administered Dose
Urine	-	32.75	-	35.06
Faeces	-	53.32	-	50.66
Cage wash	-	5.259	-	3.325
Milk fat fraction	0.9199	0.017	0.3349	0.009
Milk aqueous fraction	0.08017	0.026	0.06499	0.029
Kidney	0.07176	0.08	0.105	0.013
Liver	0.435	0.323	0.356	0.384
Muscle (flank)	0.007117	0.003	0.005472	0.001
Muscle (loin)	0.004965	0.001	0.004395	<0.001
Omental fat	0.05215	0.031	0.01549	0.012
Renal fat	0.05442	0.035	0.01240	0.005
Subcutaneous fat	0.04021	0.001	0.01210	<0.001
Blood	0.04392	-	0.03388	-
Plasma	0.04371	-	0.03667	-

Metabolites identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[14C-benzene]	[14C-thiophene]	[14C-benzene]	[14C-thiophene]
Milk Aqueous	Isofetamid	Not analysed	PPA	Not analysed
Milk Fat	Isofetamid	Isofetamid	PPA	PPA
Liver	-	PPA	Isofetamid, 4HP, PPA, IBA, 5-HPPA	Isofetamid, 4HP, 3-MTCAM, 5-HPPA
Kidney	-	PPA	Isofetamid, 4HP, PPA	4HP
Fat	Isofetamid	Isofetamid	-	4HP, PPA

Proposed Metabolic Scheme in Livestock



FREEZER STORAGE STABILITY	PMRA # 2273766

Plant matrices: almonds, canola (oilseed rape seeds), grapes, lettuce, potatoes and dry beans
The freezer storage stability data indicate that residues of isofetamid and the metabolite GPTC are stable at -20°C for up to 12 months.

CROP FIELD TRIALS & RESIDUE DECLINE ON GRAPE	PMRA # 2273769

Field trials were conducted in 2011 in Canada and the United States. Fifteen trials were conducted in NAFTA Growing Regions 1 (2 trials), 5 (3 trials), 10 (8 trials) and 11(2 trials). Isofetamid in a suspension concentrate formulation was applied three times as foliar broadcast sprays at a rate of 602-752 g a.i./ha/application for a seasonal application rate of 1.940 – 2.216 kg a.i./ha. The applications were made at about 10 ± 1 day intervals with the last application occurring 14-16 days before harvest.

Residue decline data show that residues of isofetamid remained relatively unchanged with increasing preharvest intervals (PHIs) from 9-24 days.

Analyte	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min. 1	Max. 1	LAFT 2	HAFT 2	Median 2	Mean 2	SD
Grape										
Isofetamid	1.940 – 2.216	14-16	15	0.117	2.56	0.119	1.94	0.727	0.751	0.50
GPTC				<0.01	0.153	<0.01	0.145	0.029	0.042	0.04
Combined residues3				0.135	2.61	0.142	2.00	0.772	0.783	0.50

1 Values based on total number of samples.
2 Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD =

Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.
3 The combined residues of isofetamid and GPTC are calculated as parent equivalents.

CROP FIELD TRIALS & RESIDUE DECLINE ON LETTUCE | PMRA # 2273771

Field trials were conducted in 2011 in Canada and the United States. Twenty six trials were conducted in NAFTA Growing Regions 1 (PA; 1 trial), 2 (NC; 1 trial), 3 (FL; 2 trials), 5 (WI, MI, ON, IL, QC, ND; 10 trials), and 10 (CA; 12 trials). Isofetamid in a suspension concentrate formulation was applied two times as foliar broadcast sprays at a target rate of 360 g a.i./ha/application for a seasonal application rate of 0.699 to 0.756 kg a.i./ha. The applications were made at about 10 ± 1 day intervals with the last application occurring 13-14 days before harvest.

Residue decline data show that residues of isofetamid and GPTC declined with increasing PHIs from 9-28 days.

Analyte	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min.1	Max.1	LAFT2	HAFT 2	Median2	Mean2	SD
Head Lettuce with Wrapper Leaves										
Isofetamid	699 to 756	13-14	11	<0.01	4.73	<0.01	3.44	0.292	0.594	1.0
GPTC				<0.01	0.100	<0.01	0.0994	0.0359	0.0425	0.03
Combined residues				<0.018	4.75	<0.018	3.46	0.318	0.625	1.0
Head Lettuce without Wrapper Leaves										
Isofetamid	699 to 756	13-14	11	<0.01	0.966	<0.01	0.903	<0.01	0.098	0.27
GPTC				<0.01	0.0314	<0.01	0.0289	<0.01	0.0133	0.006
Combined residues				<0.018	0.975	<0.018	0.912	0.0205	0.108	0.27
Leaf Lettuce										
Isofetamid	699 to 756	13-14	12	<0.01	5.18	<0.01	4.92	0.116	0.722	1.4
GPTC				<0.01	0.283	<0.01	0.276	0.0199	0.0835	0.10
Combined residues3				<0.018	5.26	0.0194	5.00	0.127	0.784	1.4

1 Values based on total number of samples.
2 Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.
3 The combined residues of isofetamid and GPTC are calculated as parent equivalents.

CROP FIELD TRIALS & RESIDUE DECLINE ON CANOLA | PMRA # 2273770

Field trials were conducted in 2011 in Canada and the United States. Seventeen trials were conducted in NAFTA Growing Regions 2 (NC; 1 trial), 5 (ND; 2 trials), 7 (ND; 2 trials), 9 (WA, ID & OR; 3 trials) and 14 (AB, SK & MB; 9 trials). Isofetamid in a suspension concentrate formulation was applied two times as foliar broadcast sprays at a target rate of 300 g a.i./ha/application for a seasonal application rate of 593-614 g a.i./ha. The applications were made at about 6-29 day intervals with the last application occurring 27-60 days before harvest.

Residue decline data show that no apparent trend for residues of isofetamid with increasing PHIs from 22-46 days.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min.1	Max.1	LAFT2	HAFT2	Median2	Mean2	SD
Rapeseeds										
Isofetamid	593 - 614	27-60	17	<0.01	0.0116	<0.01	0.0111	0.01	0.01	0
GPTC				<0.01	0.0116	<0.01	0.0111	0.01	0.01	0

Combined residues3				<0.018	<0.019	<0.018	<0.018	<0.018	<0.018	0

1 Values based on total number of samples.
2 Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.
3 The combined residues of isofetamid and GPTC are calculated as parent equivalents.

CROP FIELD TRIALS & RESIDUE DECLINE ON STRAWBERRY | PMRA # 2273767

Field trials were conducted in 2011 in Canada and the United States. Eleven trials were conducted in NAFTA Growing Regions 1 (1 trial), 2 (1 trial), 3 (1 trial), 5 (4 trials), 10 (3 trials) and 12 (1 trial). Isofetamid in a suspension concentrate formulation was applied five times as foliar broadcast sprays at a target rate of 467 g a.i./ha/application for a seasonal application rate of 2.307 - 2.370 kg a.i./ha. The applications were made at about 7±1 day intervals with the PHI of 0 day.

Residue decline data show that residues of isofetamid declined from 0.465 ppm to 0.0623 ppm over a 7-day span with PHIs of 0-7 days. Residues of the metabolite GPTC were in the range of <LOQ to 0.0121 ppm over the same period with no observable decline or increase pattern.

Analyte	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min.1	Max.1	LAFT2	HAFT2	Median2	Mean2	SD
Strawberry										
Isofetamid	2.307 - 2.370	0	11	0.129	3.05	0.162	2.67	0.495	0.744	0.7
GPTC				<0.01	0.0279	<0.01	0.024	<0.01	0.0124	0.005
Combined residues3				0.137	3.06	0.170	2.68	0.511	0.753	0.7

1 Values based on total number of samples.
2 Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.
3 The combined residues of isofetamid and GPTC are calculated as parent equivalents.

CROP FIELD TRIALS & RESIDUE DECLINE ON ALMOND | PMRA # 2273768

Five trials were conducted in the United States in Zone 10 (CA; 5 trials) during the 2011 growing season. Isofetamid in a suspension concentrate formulation was applied four times as foliar broadcast sprays at a target rate of 500 g a.i./ha/application for a seasonal application rate of 1.992 to 2.020 kg a.i./ha. The applications were made at 9-14 days of intervals with the last application occurring 158-217 days before harvest.

Residue decline data show that residues of isofetamid declined in almond hull with increasing PHIs from 159-179 days. Residues of the metabolite GPTC were also observed to decline in almond hull over a period of 30 days (PHIs 159-189). Residues were not detected in nutmeat at any time point (<0.01 ppm).

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min.1	Max.1	LAFT2	HAFT2	Median2	Mean2	SD
Almond Hulls (Received Basis)										
Isofetamid	1.993 to 2.021	158-217	5	<0.01	0.23	<0.01	0.21	0.01	0.05	0.09
GPTC				0.033	0.15	0.033	0.14	0.04	0.06	0.05
Combined residues				0.035	0.35	0.035	0.31	0.04	0.09	0.12
Almond Hulls (Dry Weight Basis)										
Isofetamid	1.993 to 2.021	158-217	5	<0.01	0.46	<0.01	0.41	<0.01	0.09	0.18
GPTC				0.038	0.31	0.041	0.27	0.053	0.10	0.10
Combined residues				0.037	0.68	0.043	0.61	0.053	0.17	0.25

Almond Nutmeat										
Isofetamid	1.993 to 2.021	158-217	5	<0.01	<0.01	<0.01	<0.01	0.01	0.01	0
GPTC				<0.01	<0.01	<0.01	<0.01	0.01	0.01	0
Combined residues3				<0.018	<0.018	<0.018	<0.018	0.018	0.018	0

1 Values based on total number of samples.
2 Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.
3 The combined residues of isofetamid and GPTC are calculated as parent equivalents.

RESIDUE DATA IN ROTATIONAL CROPS: Lettuce or soybean, wheat, turnip	PMRA # 2273774

Two trials (two each for turnip, lettuce/soybean and wheat) were conducted during the 2011-2012 growing season in NAFTA Growing Regions 2 and 4. Isofetamid in suspension formulation was applied three times to the primary crop, with a 13-14 day interval between applications, as a broadcast foliar application at 755-782 g a.i./ha/application, for total rates of 2.27-2.31 kg a.i./ha. Representative root and tuber, leafy and small grain crops were planted back at target intervals of 30, 120 and 365 days (30-, 120- and 365-day PBIs) and harvested at normal maturity.

No separate residue definition is necessary for the rotational crops.

Commodity	Total Application Rate (kg a.i./ha)	PBI (days)	Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Isofetamid										
Wheat Forage	2.03-2.07	29-32	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Wheat Straw	2.03-2.07	29-32	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Wheat Grain	2.03-2.07	29-32	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Soybean Forage	2.03-2.07	32	1	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Turnip Tops	2.03-2.07	29-32	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Turnip Roots	2.03-2.07	29-32	2	<0.01	0.010	<0.01	0.010	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Kale	2.03-2.07	131	1	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Leaf Lettuce	2.05-2.06	29	1	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120	1	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
GPTC										
Wheat Forage	2.03-2.07	29-32	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Wheat Straw	2.03-2.07	29-32	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Wheat Grain	2.03-2.07	29-32	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Soybean Forage	2.03-2.07	32	1	<0.01	<0.01	<0.01	<0.01	NA	NA	NA

Turnip Tops	2.03-2.07	29-32	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Turnip Roots	2.03-2.07	29-32	2	<0.01	<0.01	<0.01	<0.010	NA	NA	NA
		120-131	2	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Kale	2.03-2.07	131	1	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Leaf Lettuce	2.05-2.06	29	1	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
		120	1	<0.01	<0.01	<0.01	<0.01	NA	NA	NA
Malonyl-GPTC										
Wheat Forage	2.03-2.07	29-32	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
		120-131	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
Wheat Straw	2.03-2.07	29-32	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
		120-131	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
Wheat Grain	2.03-2.07	29-32	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
		120-131	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
Soybean Forage	2.03-2.07	32	1	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
Turnip Tops	2.03-2.07	29-32	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
		120-131	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
Turnip Roots	2.03-2.07	29-32	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
		120-131	2	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
Kale	2.03-2.07	131	1	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
Leaf Lettuce	2.05-2.06	29	1	<0.025	<0.025	<0.025	<0.025	NA	NA	NA
		120	1	<0.025	<0.025	<0.025	<0.025	NA	NA	NA

Values based on total number of samples.
* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.

Based on the results of the field accumulation study, a plant-back interval of 30 days is required for all crops not listed on the label.

PROCESSED FOOD AND FEED - GRAPE	PMRA # 2273778
Test Site	Five trials in Europe
Treatment	Broadcast foliar applications
Rate	1200 g a.i./ha
End-use product/formulation	IKF-5411 400 SC
Preharvest interval	21 days
Processed Commodity	Average Processing Factor
Raisin	2.3x
Juice	0.16x

Young wine at bottling	0.32x	
Aged wine- 6 months after bottling	0.28x	
PROCESSED FOOD AND FEED - CANOLA		PMRA # 2273770
Test Site	One trial in the US (NAFTA Region 7)	
Treatment	Broadcast foliar applications	
Rate	6.139 kg .a.i./ha	
End-use product/formulation	IKF-5411 400 SC	
Preharvest interval	33 days	
Processed Commodity	Average Processing Factor	
Canola oil	2.0x	
Canola meal	0.22x	
LIVESTOCK FEEDING – Dairy cattle and Laying hens		PMRA # 2273874
A study waiver request was provided indicating no significant residues of isofetamid and the metabolite GPTC will be in the animal commodities based on the residue magnitude in feeding commodities and the feeding level in the animal metabolism studies.		

Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES					
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops: all crops** **Rotational crops: all crops**	Isofetamid				
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops: all crops** **Rotational crops: all crops**	Isofetamid and GPTC				
METABOLIC PROFILE IN DIVERSE CROPS	Similar in grape, lettuce and French bean.				
ANIMAL STUDIES					
ANIMALS	**Ruminant and Poultry**				
RESIDUE DEFINITION FOR ENFORCEMENT	Poultry and ruminant: Isofetamid				
RESIDUE DEFINITION FOR RISK ASSESSMENT	Poultry: Isofetamid Ruminant: Isofetamid and PPA				
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	Similar profiles.				
FAT SOLUBLE RESIDUE	Yes				
DIETARY RISK FROM FOOD AND WATER					
Chronic non-cancer dietary exposure analysis **ADI = 0.05 mg/kg bw/day** **Estimated chronic drinking water concentration = 32 μg/L yearly**	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**			
		Food Alone		**Food and Water**	
		Basic	**Intermediate**	**Basic**	**Intermediate**
	All infants < 1 year	7.0	0.4	11.4	4.8
	Children 1–2 years	25.9	2.4	27.9	4.4
	Children 3 to 5 years	18.1	1.8	19.9	3.7
	Children 6–12 years	9.0	0.9	10.3	2.2

	Youth 13–19 years	4.8	0.4	5.8	1.4
	Adults 20–49 years	4.8	0.4	6.1	1.7
	Adults 50+ years	4.7	0.5	6.0	1.8
	Females 13-49 years	5.1	0.5	6.4	1.7
	Total population	6.5	0.6	7.9	2.0
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.3 mg/kg bw for Females 13+** **Estimated acute drinking water concentration = 104 µg/L daily**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**			
		Food Alone		**Food and Water**	
	Females 13-49 years	3.95		4.83	

Table 7 Fate and Behaviour in the Environment

PMRA Study Number	Study Title	Study Endpoints
2273880	Title: [14C]IKF-5411: HYDROLYTIC STABILITY	hydrolytically stable at pH values of 4, 7, and 9 at 50°C (5 days). In accordance with the guideline 10% hydrolysis at 50°C over 5 days corresponds to a DT-50 of more than a year at 25°C and for substances that hydrolyse less than this, no further testing is required
2273881	Title: [14C]IKF-5411: PHOTODEGRADATION ON SOIL SURFACE	Soil type: silt loam Dark: Half-life/DT50 for - dry soil: no degradation; moist soil 66 – 80 days Irradiated: Half-life/DT50: (both labels); moist soil: 267 days Major transformation products: none Minor transformation products:4HP (N-[1,1-dimethyl-2-(4-hydroxy-2-methylphenyl)-2-oxoethyl]-3-methyl-2-thiophenecarboxamide); 3-MTCA (3-methyl-2-thiophenecarboxylic acid); 3-MTCAM (3-methyl-2-thiophenecarboxamide), PPA (2-[3-methyl-4-[2-methyl-2-(3-methylthiophene-2-carboxamido)propanoyl]phenoxy]propanoic acid); IBA (2-methyl-4-(2-propyloxy)benzoic acid)
2273882	Title: [14C]IKF-5411: PHOTODEGRADATION AND QUANTUM YIELD IN STERILE, AQUEOUS SOLUTION	sterilised pH 7 buffer DT_{50}=1.8 days Natural water: DT_{50}=1.4 days

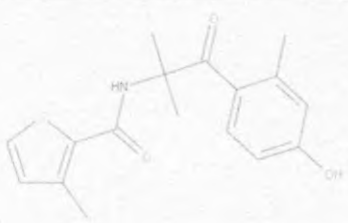
PMRA Study Number	Study Title	Study Endpoints
2273884	Title: [14C]IKF-5411: THE RATE OF DEGRADATION IN THREE SOILS UNDER AEROBIC CONDITIONS	Speyer 5M Half-life = 24.5 days (IORE; 20°C) DT50 = 20.5 days; DT90 = 81.3 days SK 15556090 Half-life = 50.6 days (20°C;DFOP) DT50 = 32.5 days; DT90 = 149 days TL78517228 Half-life = 66.2 (20°C; IORE) DT50 = 51.8 days; DT90 = 220 days
2273883	Title: [14C]IKF-5411: AEROBIC SOIL METABOLISM AND DEGRADATION - AMENDED REPORT	RC-PF Half-life = 46 days (IORE; 20°C) DT50 = 36.6 days; DT90 = 153 days
2273885	Title: [14C]IKF-5411: THE RATE OF DEGRADATION IN ONE SOIL AT 10°C UNDER AEROBIC CONDITIONS	SK 15556090 Half-life = 187 days (10°C;DFOP) DT50 = 95.5 days; DT90 = 519 days
2273886	Title: [14C]IKF-5411: ANAEROBIC SOIL METABOLISM AND DEGRADATION	RC-PF Half-life = 200 days (SFO) DT50 = 572 days DT90 = 1899 days
2273887	Title: [14C]IKF-5411: DEGRADATION IN WATER-SEDIMENT SYSTEMS UNDER AEROBIC CONDITIONS	**Parent Only** **Surface water** Calwich Abbey DT50 = 8.83 DT90 = 70.5 t_R IORE: 21.2 Swiss Lake DT50 = 20.7 DT90 = 112 slow $t_{1/2}$: 39.9 (DFOP) **Total system** Calwich Abbey DT50 = 175 DT90 = 580 Half-life = 175 (SFO) Swiss Lake DT50 = 114 DT90 = 379 Half-life =114 (SFO) **Parent plus transformation products**

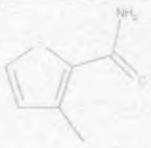
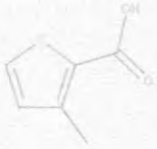
PMRA Study Number	Study Title	Study Endpoints
		Surface water Calwich Abbey DT50 = 8.5 DT90 = 125 slow $t_{1/2}$: 58.7 (DFOP) Swiss Lake DT50 = 24.2 DT90 = 299 slow $t_{1/2}$: 123 (DFOP) **Total system** Calwich Abbey DT50 = 536 DT90 = 1781 Half-life = 536 (SFO) Swiss Lake DT50 = 380 DT90 = 1262 Half-life =380 (SFO)
2273888	Title: [14C]IKF-5411: DEGRADATION IN WATER-SEDIMENT SYSTEMS UNDER ANAEROBIC CONDITIONS	**Surface water** Goose River DT50 = 34.5 DT90= 132 t_R IORE: 58 Golden Lake DT50 = 70.1 DT90 = 531 t_R IORE: 160 **Total System** Goose River DT50 = 2186 DT90= 65936 t_R IORE: 19800 Golden Lake DT50 = 1944 DT90 = 6457 Half-life = 1944 (SFO)
2273889	Title: [14C]IKF-5411: ADSORPTION/DESORPTION IN FIVE SOILS	RC-PF loamy sand (1.1% OC; pH 6.9; CEC: 13.4; 85% sand) K_d=6.59 K_{oc}=598 K_f=6.64 K_{foc} = 602.6 1/n = 0.873 EL_7 loam (2.9% OC; pH 6.5; CEC: 37.2; 31% sand) K_d=17.84 K_{oc}=615.2

PMRA Study Number	Study Title	Study Endpoints
		K_f=17.17 K_{foc} = 591.9 1/n = 0.921 SK179618 silt loam (3.9% OC; pH 5; CEC: 23.3; 30% sand) K_d=19.43 K_{oc}=499.9 K_f=20.79 K_{foc} = 534.9 1/n = 0.991 SK961089 clay loam (5% OC; pH 7.4; CEC: 40.9; 38% sand) K_d=14.02 K_{oc}=281.1 K_f=13.68 K_{foc} = 274.3 1/n = 0.924 Saitama sandy loam (3.3% OC; pH 5.5; CEC: 13.4; 60% sand) K_d=15.17 K_{oc}=458.9 K_f=14.86 K_{foc} = 449.6 1/n = 0.933
2273890	Title: 4HP (METABOLITE OF IKF-5411): ADSORPTION/DESORPTION IN FIVE SOILS	EL-7 loam (2.9% OC; pH 6.5; CEC: 37.2; 31% sand) K_d= 8.90 K_{oc}= 307 K_f= 8.71 K_{foc} = 300.3 1/n = 0.872 Saitama sandy loam (3.3% OC; pH 5.5; CEC: 13.4; 60% sand) K_d=4.12 K_{oc}= 133 K_f= 3.90 K_{foc} = 126 1/n = 0.93
2273787	Title: Terrestrial Field Dissipation of IKF-5411 Applied to Bareground in Northwood, ND - USA 2010	Location/soil type: Northwood, North Dakota; sandy loam from 0-46 cm. DT50: 6.98 days DT90: 126 days Transformation products detected: 4-HP
2273788	Title: Terrestrial Field Dissipation of IKF-5411 Applied to Bareground in Aberdeen, SK, Canada - 2010	**Location/soil type:** Aberdeen, Saskatchewan/clay loam **Half-life/DT50:** 217 days (3 applications) **DT90:** 990 days **Major transformation products detected:** 4-HP **Half-life/DT50:** 46.4 days **DT90:** 536 days

PMRA Study Number	Study Title	Study Endpoints
2273789	Title: Field Soil Dissipation for Isofetamid 400SC Applied to Turf in Proctor, AR - USA 2011	Location/soil type: Proctor, AR/silt loam Half-life: 35 days DT90: not estimated Major transformation products detected: 4-HP
2273785	Terrestrial Field Dissipation of IKF-5411 Applied to Bareground in Kerman, CA - USA 2010	Location/soil type: Kerman, CA - loamy sand soil DT_{50}: 46.5 days (SFO) DT_{90}: 155 days (SFO) Major transformation products detected: none
2273791	Title: Field Soil Dissipation for Isofetamid 400SC Applied to Turf in Goldsboro, NC - USA 2011	Location/soil type:Pikeville, NC fescue turfgrass (Kentucky 31) grown on sandy loam Half-life/DT50: 29 days (based on the last application) DT90: not calculated Major transformation products detected: 4-HP

Table 8 Transformation Products of Isofetamid

Structure	Transformation Product name (Nomenclature)	Study Type	Max % of Applied, days after treatment (DAT)	PMRA Number(s)
	4HP (N-[1,1-dimethyl-2-(4-hydroxy-2-methylphenyl)-2-oxoethyl]-3-methyl-2-thiophenecarboxamide)	Aerobic soil	9.2% AR, 30 DAT	2273883 2273884 2273885
		Aerobic aquatic	6.6% AR, 100 DAT	2273887
		Anaerobic soil	9.5% AR, 150 DAT	2273886
		Anaerobic aquatic	2.5% AR, 365 DAT	2273888
		Photolysis – buffer	-	
		Photolysis – soil	2.8% AR, 21 DAT	2273881
		Field dissipation	ND: App 3 21 DAT = 0.016 ppm SK: App 3 282 DAT= 0.025 ppm	2273787 2273788 2273789 2273785 2273791
	PPA (2-[3-methyl-4-[2-methyl-2-(3-methylthiophene-2-carboxamido)propanoyl] phenoxy]propanoic acid)	Aerobic soil	3.7% AR, 7 DAT	2273883 2273884 2273885
		Aerobic aquatic	10.9% AR, 100 DAT	2273887
		Anaerobic soil	1.7% AR, 120 DAT	2273886
		Anaerobic aquatic	3.3% AR, 365 DAT	2273888
		Photolysis – buffer	10.9% AR at 7 DAT	2273882

		Photolysis – soil	1.7% AR, 21 DAT	2273881
		Field dissipation		2273787 2273788 2273789 2273785 2273791
	3-MTCAM (3-methyl-2-thiophenecarboxamide)	Aerobic soil	0.5% AR, 14DAT	2273883 2273884 2273885
		Aerobic aquatic	0.7%, 0 DAT	2273887
		Anaerobic soil	Not confirmed	2273886
		Anaerobic aquatic	0.9% AR, 0 DAT	2273888
		Photolysis – buffer	35.6% AR, 4 DAT	2273882
		Photolysis – soil	5.5% AR, 14 DAT	2273881
		Field dissipation		2273787 2273788 2273789 2273785 2273791
	3-MTCA (3-methyl-2-thiophenecarboxylic acid) *It should be noted that 3-MTCA is a synthetic impurity with an upper certified limit of 0.2% (w/w) PMRA 2273822*	Aerobic soil	2.2% AR, 59 DAT	2273883 2273884 2273885
		Aerobic aquatic	1.2% AR, 30 DAT	2273887
		Anaerobic soil	Not confirmed	2273886
		Anaerobic aquatic	0.6% AR, 14 DAT	2273888
		Photolysis – buffer	*Not classed as major but is the sequential transformation step of 3-MTCAM -> 3-MTCA formed at 7.1% AR at 4 DAT*	2273882
		Photolysis – soil	1.5% AR, 21 DAT	2273881
		Field dissipation		2273787 2273788 2273789 2273785 2273791

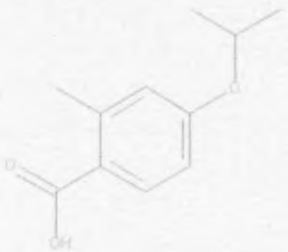
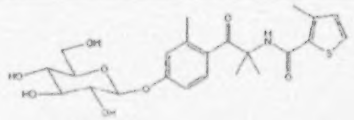
	IBA	Aerobic soil		2273883 2273884 2273885
		Aerobic aquatic	3.7% AR, 59 DAT	2273887
		Anaerobic soil	Not confirmed	2273886
		Anaerobic aquatic	1.0% AR, 59 DAT	2273888
		Photolysis – buffer	79.7% AR 10 DAT	2273882
		Photolysis – soil	4.7% AR, 30 DAT	2273881
		Field dissipation		2273787 2273788 2273789 2273785 2273791
	GPTC (plant metabolite)	Field Dissipation	For both turf studies at NC and AR: <1% at all sampling points	2273789 2273791

Table 9 Effects on Non-Target Species

PMRA Study Number	Study Title	Study Endpoints
2273893	Title: IKF-5411 TECHNICAL ACUTE TOXICITY (LC50) TO THE EARTHWORM	LC50: >1000 mg a.i./kg dw soil EC50: >1000 mg a.i./kg dw soil NOAEC: 309 mg a.i./kg dw soil Endpoint(s) Affected: body weight loss (%)
2273795	Title: Isofetamid 400SC ACUTE TOXICITY TO HONEY BEES	Acute Oral: LC50 >100 µg a.i./bee Acute contact: LD50 >100 µg a.i./bee
2273895	Title: IKF-5411 TECHNICAL ACUTE TOXICITY TO HONEY BEES	LD50 =100 µg a.i./bee (contact) 95% C.I. 75.2 – 411 ug a.i./bee NOEL: 22.66 ug a.i./bee (mortality) LC50 >30 µg a.i./bee (oral) NOEC: 30 ug a.i./bee
2273796	Title: IKF-5411 400 SC ACUTE TOXICITY TO TYPHLODROMUS PYRI IN THE LABORATORY	7-d LR_{50}: > 1000 g a.i./ha Endpoint: Mortality NOER = 250 g a.i./ha Endpoint: mortality

PMRA Study Number	Study Title	Study Endpoints
2273797	Title: Isofetamid 400SC ACUTE TOXICITY TO APHIDIUS RHOPALOSIPHI IN THE LABORATORY	48-h LR_{50}: > 1000 g a.i./ha Endpoint affected: none NOER = 1000 g a.i./ha Endpoint affected: none
2273798	Title: A 48-HOUR ACUTE IMMOBILIZATION STUDY OF Isofetamid 400SC IN DAPHNIA MAGNA	EC_{50}: 8.5 mg a.i./L 95% C.I.: 5.7-12 mg a.i./L NOEC: 3.2 mg a.i./L Probit Slope: 2.06665 Endpoint(s) Affected: Mobility, lethargy or activity.
2273896	Title: A 48-HOUR ACUTE IMMOBILIZATION STUDY OF IKF-5411 TECHNICAL WITH DAPHNIA MAGNA	EC50:4.7 mg a.i./L 95% C.I.: 4.3 – 5.1 mg a.i./L NOEC:3.5 mg a.i./L Probit Slope: 10.76 Endpoint(s) Affected: Mobility, lethargy or activity
2273897	Title: DAPHNIA MAGNA REPRODUCTION STUDY OF IKF-5411 TECHNICAL	NOAEC: <0.39 mg ai/L LOAEC: 0.39 mg ai/L Endpoints affected: length, dry weight, and reproduction Most sensitive endpoint(s): length
2273898	Title: [14C]-IKF-5411: SEDIMENT-WATER CHIRONOMUS RIPARIUS TOXICITY TEST USING SPIKED SEDIMENT	Endpoint(s) affected: emergence success Most sensitive endpoint(s): emergence success <u>Based on initial measured sediment concentrations:</u> EC_{50} (emergence ratio) >993 mg a.i/kg LOAEC (emergence ratio): 993 mg a.i/kg NOAEC (emergence ratio): 483mg a.i/kg EC_{50} (development rate): >993 mg a.i/kg LOAEC (development rate): >993 mg a.i/kg NOAEC (development rate): 993 mg a.i/kg
2273899	Title: IKF-5411 TECHNICAL: A 96-HOUR FLOW-THROUGH ACUTE TOXICITY TEST WITH THE SALTWATER MYSID	Test: Flow-through 96-hr LC50 = 1.51 mg a.i./L, 95% C.I. = n/a NOEC = 0.64 mg a.i./L Endpoints effected: mortality
2273900	Title: IKF-5411 TECHNICAL: A 96-HOUR SHELL DEPOSITION TEST WITH THE EASTERN OYSTER	96 hour EC_{50} = 0.44 mg a.i./L (95% C.I. = 0.326 – 0.604 mg a.i./L) NOAEC = 0.030 mg a.i./L

PMRA Study Number	Study Title	Study Endpoints
		Endpoints effected: inhibition of shell growth.
2273901	Title: IKF-5411 Technical ACUTE TOXICITY TO RAINBOW TROUT	96 h LC50: 2.27 mg a.i/L 95% C.I.:1.72 – 3.04 mg a.i /L 96 h NOEC:0.528 mg a.i /L Probit Slope:N/A LOEC: 1.07mg a.i /L Endpoint(s) Effected:Mortality and sub-lethal effects
2273902	Title: IKF-5411 TECHNICAL: A 96-HOUR FLOW-THROUGH ACUTE TOXICITY TEST WITH THE BLUEGILL	96 h LC50: >3.2 mg a.i/L 95% C.I.: N/A 96 h NOEC: 3.2 mg a.i /L Probit Slope: N/A Endpoint(s) Effected:There were no compound related effects (survival or sublethal) noted during this study
2273799	Title: A 96-HOUR ACUTE TOXICITY STUDY OF Isofetamid 400SC IN COMMON CARP	LC50: 35 mg a.i/L 95% C.I.: 23-54 mg a.i./L) Endpoint(s) Effected: mortality NOEC: could not be determined 96-hr LOEC (muscle spasms, curved body scoliosis, hemorrhaging, and complete loss of equilibrium) = 5.5 mg a.i./L
2273903	Title: A 96-HOUR ACUTE TOXICITY STUDY OF IKF-5411 TECHNICAL WITH COMMON CARP	LC50: > 6.8 mg a..i./L NOEC: 2.4 mg a.i./L Endpoint affected: sub-lethal effects (fish swimming at the surface, losing equilibrium, having Scoliosis (curved bodies), having exophthalmia, having hemorrhaging, partially losing equilibrium, or having reduced activity)
2273904	Title: IKF-5411 TECHNICAL: A 96-HOUR FLOW-THROUGH ACUTE TOXICITY TEST WITH THE SHEEPSHEAD MINNOW	A definitive 96 hour LC50 could not be determined but instead was estimated as >2.8 mg a.i./L using mean measured concentrations and the NOEC was 2.8 mg a.i./L (mean-measured), based on mortality.
2273905	Title: IKF-5411 TECHNICAL: AN EARLY LIFE-STAGE TOXICITY TEST WITH THE FATHEAD MINNOW	Growth (Length); (most sensitive endpoint): NOAEC: 0.086 mg ai/L LOAEC: 0.18 mg ai/L

PMRA Study Number	Study Title	Study Endpoints
2273906	Title: IKF-5411 TECHNICAL ACUTE ORAL TOXICITY (LD50) TO THE BOBWHITE QUAIL	LD50: >2000 mg a.i./kg bw95% C.I.: n/a Probit slope: N/A NOAEL (mortality): 2000 mg a.i./kg bw LOAEL (mortality): >2000 mg a.i./kg bw NOAEL (weight gain): 500 mg a.i./kg bw (male) and <500 mg a.i. /kg bw (female) LOAEL (weight gain): 1000 mg a.i./kg bw (male) and 500 mg a.i./kg bw (female) Endpoint(s) Affected: Body weight gain
2273907	Title: IKF-5411 TECHNICAL: ACUTE ORAL TOXICITY (LD50) TO THE MALLARD DUCK	Endpoints not valid, no definitive study was conducted – *will use canary results instead*
2273908	Title: IKF-5411 TECHNICAL: AN ACUTE ORAL TOXICITY STUDY WITH THE CANARY (Serinus canaria)	LD_{50} > 2000 mg a.i./kg bw, NOEL > 2000 mg a.i./kg bw
2273909	Title: IKF-5411 TECHNICAL DIETARY TOXICITY (LC50) TO THE BOBWHITE QUAIL	LC50: >5180 mg a.i./kg diet (892 mg a.i./kg bw/day) 95% C.I.: N/A NOAEC: 5180 mg a.i./kg diet LOAEC: >5180 mg a.i./kg diet Endpoints affected: none
2273910	Title: IKF-5411 TECHNICAL DIETARY TOXICITY (LCSO) TO THE MALLARD DUCK	LC50: >4930 mg a.i./kg diet (1582 mg a.i./kg bw/day) 95% C.I.: N/A NOAEC: 4930 mg a.i./kg diet LOAEC: >4930 mg a.i./kg diet Endpoints affected: none
2273911	Title: IKF-5411 ASSESSMENT TO DETERMINE THE EFFECTS ON REPRODUCTION IN THE BOBWHITE QUAIL	NOEC:276 mg a.i./kg-diet (mean measured); 6.05 mg a.i./kg-bw (females) and 7.88 mg a.i./kg-bw (males) LOEC:276 mg a.i./kg-diet (mean measured); 25 mg a.i./kg-bw Endpoint Effected: overall reproductive success, specifically, a reduced number of normal hatchlings
2273912	Title: IKF-5411 TECHNICAL ASSESSMENT TO DETERMINE THE EFFECTS ON REPRODUCTION IN THE MALLARD DUCK	NOAEC: 285 mg ai/kg; 34 mg/kg bodyweight/day in males and 35 mg/kg bodyweight/day in females LOAEC: 928 mg ai/kg; 119 mg/kg bodyweight/day in males and 121 mg/kg bodyweight/day in females Endpoints affected: Eggshell thickness

PMRA Study Number	Study Title	Study Endpoints
2273913	Title: IKF-5411 TECHNICAL: A 96-HOUR TOXICITY TEST WITH THE FRESHWATER ALGA (ANABAENA FLOS-AQUAE)	Endpoints not reliable
2273914	Title: IKF-5411 TECHNICAL: A 96-HOUR TOXICITY TEST WITH THE FRESHWATER ALGA (PSEUDOKIRCHNERIELLA SUBCAPITATA)	Test Type: Static 96 hr EC20: 4.1 mg a..i./L 95% C.I.: 2.47 to >4.3 mg a.i./L 96 hr EC50: >4.3 mg a.i./L 95% C.I.: n/a 96 hr NOEC: 1.2 mg a.i./L Probit Slope: 0.99253 Endpoints Effected: cell density
2273915	Title: IKF-5411 TECHNICAL: A 96-HOUR TOXICITY TEST WITH THE FRESHWATER DIATOM (Navicula pelliculosa)	96 hr EC50 : >4.8 mg a.i./L95% C.I.: n/a 96 hr NOEC: 0.41 mg a.i./L Endpoints Effected: cell density, yield and growth rate
2273916	Title: IKF-5411 TECHNICAL: A 96-HOUR TOXICITY TEST WITH THE MARINE DIATOM (Skeletonema costatum)	$EC50_{yield}$ = 0.90 mg a.i./L 95% C.I.: 0.33 – 2.46 96 hour NOEC: 0.05 mg a.i./L Probit Slope: n/a 95% C.I.: n/a
2273918	Title: Isofetamid 400SC Terrestrial (Non-target) Plant Growth Test Seedling Emergence	**PMRA** **Monocot** EC25: 851 mg a.i./kg; 95% C.I. = 285-8940 (ryegrass) EC50: >1000 mg a.i/kg (all species) EC05: 33.2 mg a.i./kg; 95% C.I. = 0.0497 – 361 (ryegrass) NOEC <62.5 mg a.i./kg (onion) Most sensitive monocot: Perennial ryegrass (Lolium perenne) based on dry weight **Dicot** EC25: 16.1 mg a.i/kg; 95% C.I. 2.18 – 78.7 (tomato) EC50: 246 mg a.i/kg; 95% C.I. 87.3 – 754 (tomato) EC05: 0.164 mg a.i./kg; 95% C.I. 0.00194 –4.12 (tomato) NOEC: <62.5 mg a.i./kg (cucumber, lettuce, soybean) Most sensitive dicot: Tomato (Lycopersicon

PMRA Study Number	Study Title	Study Endpoints
		esculentum) based on dry weight **EPA** **Monocot** EC_{50}/IC_{50}: 4920 lb ai/A 95% C.I.: 433-55900 lb ai/A EC_{25}/IC_{25}: 576 lb ai/A; 95% C.I.: 255-1150 lb ai/A EC_{05}/IC_{05}: 26.3 lb ai/A; 95% C.I.: N/A-110 lb ai/A NOEC: 83.675 lb ai/A **Dicot** EC_{50}/IC_{50}: 168 lb ai/A; 95% C.I.: 92.8-303 lb ai/A EC_{25}/IC_{25}: 10.3 lb ai/A; 95% C.I.: 3.94-23.7 lb ai/A EC_{05}/IC_{05}: 0.188 lb ai/A; 95% C.I.: N/A-2.57 lb ai/A NOEC: 2.615 lb ai/A The most sensitive monocot was ryegrass based on dry weight, with NOAEC and EC_{25} values of 83.675 and 576 lb ai/A, respectively. The most sensitive dicot was tomato, based on dry weight, with NOAEC and EC_{25} values of 2.615 and 10.3 lb ai/A, respectively.
2273919	Title: Isofetamid 400SC Terrestrial (Non-target) Plant Growth Test Vegetative Vigour	**PMRA** **Monocot** EC25:>1200 g a.i./ha (all species) EC50: 1711 g a.i./ha (corn) EC05: 217 g a.i/ha (onion) NOEC 1200 g a.i./ha (all species) Most sensitive monocot: Corn (*Zea mays*) based on dry weight **Dicot** EC25: 1366 g a.i./ha (soybean) EC50: >1200 g a.i./ha (all species) EC05: 121 g a.i./ha (carrot) NOEC: 1200 g a.i./ha (all species) Most sensitive dicot: Soybean (*Glycine max*) based on dry weight **EPA** EC_{50}/IC_{50}: Not calculable 95% C.I.: N/A

PMRA Study Number	Study Title	Study Endpoints
		EC_{25}/IC_{25}: 1.3 lb ai/A; 95% C.I.: N/A-3.47 lb ai/A EC_{05}/IC_{05}: 0.766 lb ai/A; 95% C.I.: N/A-1.55 lb ai/A NOEC: 1.07 lb ai/A Slope: N/A; 95% C.I.: N/A Most sensitive dicot: soybean, dry weight EC_{50}/IC_{50}: Not calculable EC_{25}/IC_{25}: 1.26 lb ai/A; 95% C.I.: 0.448-2.58 lb ai/A EC_{05}/IC_{05}: 0.247 lb ai/A; 95% C.I.: N/A-0.614 lb ai/A NOEC: 1.07 lb ai/A; Slope: N/A The most sensitive monocot was ryegrass based on dry weight, with NOAEC and EC_{25} values of 83.675 and 576 lb ai/A, respectively. The most sensitive dicot was tomato, based on dry weight, with NOAEC and EC_{25} values of 2.615 and 10.3 lb ai/A, respectively.
2273917	Title: IKF-5411 TECHNICAL: A 7-DAY STATIC-RENEWAL TOXICITY TEST WITH DUCKWEED (Lemna gibba G3)	7 day EC_{50} > 4.9 mg a.i./L 7 day NOEC = 4.9 mg a.i./L Endpoints affected: none

Table 10 Screening Level Risk Assessment on Non-Target Species - Terrestrial Organisms, excluding birds and mammals

Organism	Exposure	PMRA Number	Endpoint value	EEC	RQ	LOC exceeded?
Invertebrates						
Earthworm	Acute	2273893	1/2 LC_{50} > 500 mg a.i./kg dry soil	1.9 mg a.i./kg dry soil	>0.004	No
Bee	Oral[1]	2273795	30 µg a.i./bee	18.7 µg a.i./bee[1]	0.6	Yes
	Contact[2]		100 µg a.i./bee	1.55 µg a.i./bee[2]	0.02	No
Predatory arthropod (*T. pyri*)	Contact	2273796	LR_{50} = 1000 g a.i./ha	1026.95 g a.i./ha (in-field)	1.03	No
				61.6 g a.i./ha (off-field)	0.06	No
Parasitic arthropod (*A. rhopalosiphi*)	Contact	2273797	LR_{50} = 1000 g a.i./ha	1026.95 g a.i./ha (in-field)	1.03	No

Organism	Exposure	PMRA Number	Endpoint value	EEC	RQ	LOC exceeded?
				61.6 g a.i./ha (off-field)	0.06	No
Vascular plants						
Vascular plant	Seedling emergence	2273918	EC_{25}= 16.1 mg a.i./kg soil or *ca* 36,250 g a.i./ha (tomato)	1.9 mg a.i./kg dry soil	0.12	No
	Vegetative vigour	2273919	EC_{25} = 1366 g a.i./ha (soybean)	1026.95 g a.i./ha	0.75	No

[1] Oral exposure as per Rortais et al (2005) and Crailsheim et al (1992 and 1993), the maximum single field application rate is converted to an amount of ai that forager bees will consume via nectar consumption rates i.e. maximum single field application rate (kg a.i./ha) multiplied by 29 µg a.i./bee per kg/ha.
[2]Contact exposure endpoint converted to field rate as per Koch and Weiber 1997, i.e. maximum single application rate in kg x 2.4 µg a.i./bee

Table 11 Screening Level Risk Assessment on Non-Target Species – Birds

	Toxicity (mg ai/kg bw/d)	Feeding Guild (food item)	EDE (mg ai/kg bw)	RQ
Small Bird (0.02 kg)				
Acute	200.00	Insectivore (small insects)	51.75	0.26
Reproduction	6.05	Insectivore (small insects)	51.75	8.55
Medium Sized Bird (0.1 kg)				
Acute	200.00	Insectivore (small insects)	40.38	0.20
Reproduction	6.05	Insectivore (small insects)	40.38	6.67
Large Sized Bird (1 kg)				
Acute	200.00	Herbivore (short grass)	42.14	0.21
Reproduction	6.05	Herbivore (short grass)	42.14	6.96

Table 12 Screening Level Risk Assessment on Non-Target Species – Mammals

	Toxicity (mg ai/kg bw/d)	Feeding Guild (food item)	EDE (mg ai/kg bw)	RQ
Small Mammal (0.015 kg)				
Acute	200.00	Insectivore (small insects)	30.04	0.15
Reproduction	65.80	Insectivore (small insects)	30.04	0.46
Medium Sized Mammal (0.035 kg)				
Acute	200.00	Herbivore (short grass)	94.12	0.47
Reproduction	65.80	Herbivore (short grass)	94.12	1.43
Large Sized Mammal (1 kg)				
Acute	200.00	Herbivore (short grass)	50.29	0.25
Reproduction	65.80	Herbivore (short grass)	50.29	0.76

Table 13 Screening Level Risk of IKF-5411 to Aquatic Organisms

Organism	Exposure	PMRA Number	Endpoint value	EEC (mg a.i./L)	RQ	LOC exceeded?
Freshwater species						
Daphnia magna	Acute 48-h	2273896	LC_{50} = 2.35 mg a.i./L	0.53	0.226	No
	Chronic 21-day	2273897	NOEC = 0.8 mg a.i./L	0.53	0.66	No
Rainbow trout	Acute 96 hr	2273901	LC_{50} = 0.227 mg a.i./L	0.53	2.33	Yes
Bluegill sunfish	Acute 96 hr	2273902	LC_{50} > 0.32 mg a.i./L	0.53	>1.66	Yes
Fathead minnow	Chronic – Early Life Stage 5-d embryo and 28-d juvenile	2273905	NOEC = 0.86 mg a.i./L	0.53	6.16	Yes
Amphibians	Acute 96 hr	2273901	LC_{50} = 0.227 mg a.i./L (from rainbow trout acute)	2.82	12.4	Yes
	Chronic – Early Life Stage 5-d embryo and 28-d juvenile	2273905	NOEC = 0.86 mg a.i./L (from fathead minnow trout ELS)	2.82	3.28	Yes
Freshwater alga *Pseudokirchneriella subcapitata*	Acute 96 hr	2273914	EC_{50} = 2.15 mg a.i./L	0.53	0.25	No
Vascular plant Duckweed *Lemna gibba G3*	Dissolved – static renewal 7-day	2273917	EC_{50} = 2.45 mg a.i./L	0.53	0.22	No
Chironomus riparius	Chronic	2273898	NOEC = 483 mg a.i./L	0.53	0.00	No[1]
Marine species						
Mysid	Acute 96 hr	2273899	EC_{50} = 0.755 mg a.i./L	0.53	0.71	No
Mollusk *Crassostrea virginica*	Acute 96 hr	2273900	EC_{50} = 0.22 mg a.i./L	0.53	2.41	Yes
Sheepshead minnow	Acute 96 hr	2273904	LC_{50} > 0.28 mg a.i./L	0.53	>1.89	Yes
Marine alga *Skeletonema costatum*	Acute 96 hr	2273916	EC_{50} = 0.45 mg a.i./L	0.53	1.18	Yes

[1]Risk quotient based on comparison of effects concentrations for pore water against EEC in overlying water.

Table 14 Further Characterisation Risk Assessment – birds – turf application

			Maximum nomogram residues	Mean nomogram residues

	Toxicity (mg ai/kg bw/d)	Food Guild (food item)	On-field EDE (mg ai/kg bw)	RQ	Off Field EDE (mg ai/kg bw)	RQ	On-field EDE (mg ai/kg bw)	RQ	Off Field EDE (mg ai/kg bw)	RQ
Small Birds (0.02 kg)										
Acute	200.00	Insectivore (small insects)	51.75	0.26	3.10	0.02	28.86	0.14	1.73	0.01
		Granivore (grain and seeds)	12.94	0.06	0.78	0.00	6.17	0.03	0.37	0.00
		Frugivore (fruit)	25.87	0.13	1.55	0.01	12.34	0.06	0.74	0.00
Dietary	158.20	Insectivore (small insects)	51.75	0.33	3.10	0.02	28.86	0.18	1.73	0.01
		Granivore (grain and seeds)	12.94	0.08	0.78	0.00	6.17	0.04	0.37	0.00
		Frugivore (fruit)	25.87	0.16	1.55	0.01	12.34	0.08	0.74	0.00
Reproduction	6.05	Insectivore (small insects)	51.75	**8.55**	3.10	0.51	28.86	**4.77**	1.73	0.29
		Granivore (grain and seeds)	12.94	**2.14**	0.78	0.13	6.17	**1.02**	0.37	0.06
		Frugivore (fruit)	25.87	**4.28**	1.55	0.26	12.34	**2.04**	0.74	0.12
Medium Birds (0.1 kg)										
Acute	200.00	Insectivore (small insects)	40.38	0.20	2.42	0.01	22.52	0.11	1.35	0.01
		Insectivore (large insects)	10.10	0.05	0.61	0.00	4.81	0.02	0.29	0.00
		Granivore (grain and seeds)	10.10	0.05	0.61	0.00	4.81	0.02	0.29	0.00
		Frugivore (fruit)	20.19	0.10	1.21	0.01	9.63	0.05	0.58	0.00
Dietary	158.20	Insectivore (small insects)	40.38	0.26	2.42	0.02	22.52	0.14	1.35	0.01
		Insectivore (large insects)	10.10	0.06	0.61	0.00	4.81	0.03	0.29	0.00
		Granivore (grain and seeds)	10.10	0.06	0.61	0.00	4.81	0.03	0.29	0.00
		Frugivore (fruit)	20.19	0.13	1.21	0.01	9.63	0.06	0.58	0.00
Reproduction	6.05	Insectivore (small insects)	40.38	**6.67**	2.42	0.40	22.52	**3.72**	1.35	0.22
		Insectivore (large insects)	10.10	**1.67**	0.61	0.10	4.81	0.80	0.29	0.05
		Granivore (grain and seeds)	10.10	**1.67**	0.61	0.10	4.81	0.80	0.29	0.05
		Frugivore (fruit)	20.19	**3.34**	1.21	0.20	9.63	**1.59**	0.58	0.10
Large Birds (1 kg)										
Acute	200.00	Insectivore (small insects)	11.79	0.06	0.71	0.00	6.58	0.03	0.39	0.00
		Insectivore (large insects)	2.95	0.01	0.18	0.00	1.41	0.01	0.08	0.00
		Granivore (grain and seeds)	2.95	0.01	0.18	0.00	1.41	0.01	0.08	0.00
		Frugivore (fruit)	5.90	0.03	0.35	0.00	2.81	0.01	0.17	0.00
		Herbivore (short grass)	42.14	0.21	2.53	0.01	14.96	0.07	0.90	0.00
		Herbivore (long grass)	25.73	0.13	1.54	0.01	8.40	0.04	0.50	0.00
		Herbivore (forage crops)	38.99	0.19	2.34	0.01	12.89	0.06	0.77	0.00

Dietary	158.20	Insectivore (small insects)	11.79	0.07	0.71	0.00	6.58	0.04	0.39	0.00
		Insectivore (large insects)	2.95	0.02	0.18	0.00	1.41	0.01	0.08	0.00
		Granivore (grain and seeds)	2.95	0.02	0.18	0.00	1.41	0.01	0.08	0.00
		Frugivore (fruit)	5.90	0.04	0.35	0.00	2.81	0.02	0.17	0.00
		Herbivore (short grass)	42.14	0.27	2.53	0.02	14.96	0.09	0.90	0.01
		Herbivore (long grass)	25.73	0.16	1.54	0.01	8.40	0.05	0.50	0.00
		Herbivore (forage crops)	38.99	0.25	2.34	0.01	12.89	0.08	0.77	0.00
Reproduction	6.05	Insectivore (small insects)	11.79	**1.95**	0.71	0.12	6.58	1.09	0.39	0.07
		Insectivore (large insects)	2.95	0.49	0.18	0.03	1.41	0.23	0.08	0.01
		Granivore (grain and seeds)	2.95	0.49	0.18	0.03	1.41	0.23	0.08	0.01
		Frugivore (fruit)	5.90	0.97	0.35	0.06	2.81	0.46	0.17	0.03
		Herbivore (short grass)	42.14	**6.96**	2.53	0.42	14.96	**2.47**	0.90	0.15
		Herbivore (long grass)	25.73	**4.25**	1.54	0.26	8.40	**1.39**	0.50	0.08
		Herbivore (forage crops)	38.99	**6.44**	2.34	0.39	12.89	**2.13**	0.77	0.13

Table 15 Further Characterisation Risk Assessment – mammals – turf application

	Toxicity (mg ai/kg bw/d)	**Food Guild (food item)**	**Mean nomogram residues**			**RQ**
			On-field		**Off Field**	
			EDE (mg ai/kg bw)	**RQ**	**EDE (mg ai/kg bw)**	
Small Mammal (0.015 kg)						
Acute	200.00	Insectivore (small insects)	16.75	0.0838	1.01	0.0050
	200.00	Granivore (grain and seeds)	3.58	0.0179	0.21	0.0011
	200.00	Frugivore (fruit)	7.16	0.0358	0.43	0.0021
Reproduction	65.80	Insectivore (small insects)	16.75	0.2546	1.01	0.0153
	65.80	Granivore (grain and seeds)	3.58	0.0544	0.21	0.0033
	65.80	Frugivore (fruit)	7.16	0.1089	0.43	0.0065
Medium Sized Mammal (0.035 kg)						
Acute	200.00	Insectivore (small insects)	14.69	0.0734	0.88	0.0044
	200.00	Insectivore (large insects)	3.14	0.0157	0.19	0.0009
	200.00	Granivore (grain and seeds)	3.14	0.0157	0.19	0.0009
	200.00	Frugivore (fruit)	6.28	0.0314	0.38	0.0019
	200.00	Herbivore (short grass)	33.43	0.1671	2.01	0.0100
	200.00	Herbivore (long grass)	18.77	0.0938	1.13	0.0056
	200.00	Herbivore (forage crops)	28.79	0.1439	1.73	0.0086
Reproduction	65.80	Insectivore (small insects)	14.69	0.2232	0.88	0.0134
	65.80	Insectivore (large insects)	3.14	0.0477	0.19	0.0029

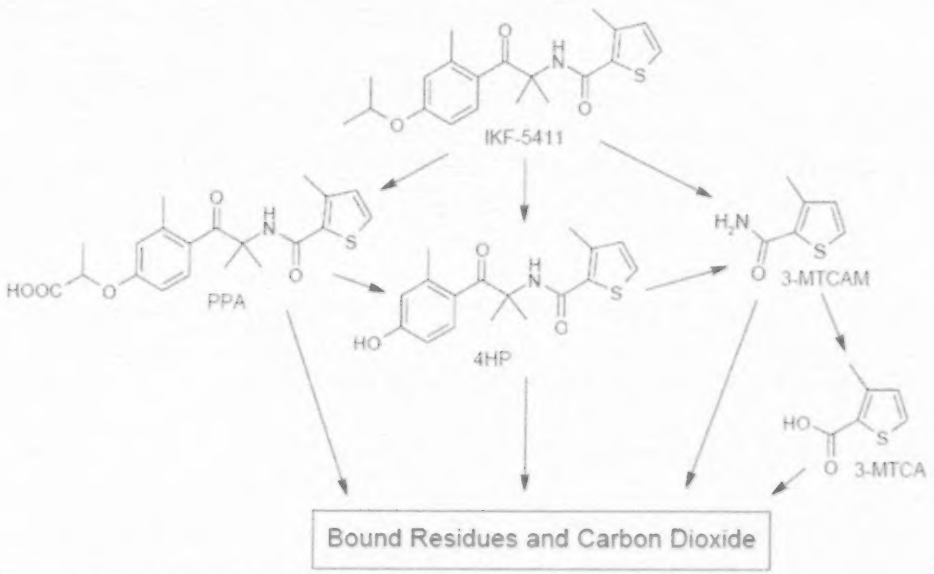
	65.80	Granivore (grain and seeds)	3.14	0.0477	0.19	0.0029
	65.80	Frugivore (fruit)	6.28	0.0954	0.38	0.0057
	65.80	Herbivore (short grass)	33.43	0.5080	2.01	0.0305
	65.80	Herbivore (long grass)	18.77	0.2852	1.13	0.0171
	65.80	Herbivore (forage crops)	28.79	0.4375	1.73	0.0263
Large Sized Mammal (1 kg)						
Acute	200.00	Insectivore (small insects)	7.85	0.0392	0.47	0.0024
	200.00	Insectivore (large insects)	1.68	0.0084	0.10	0.0005
	200.00	Granivore (grain and seeds)	1.68	0.0084	0.10	0.0005
	200.00	Frugivore (fruit)	3.36	0.0168	0.20	0.0010
	200.00	Herbivore (short grass)	17.86	0.0893	1.07	0.0054
	200.00	Herbivore (long grass)	10.03	0.0501	0.60	0.0030
	200.00	Herbivore (forage crops)	15.38	0.0769	0.92	0.0046
Reproduction	65.80	Insectivore (small insects)	7.85	0.1193	0.47	0.0072
	65.80	Insectivore (large insects)	1.68	0.0255	0.10	0.0015
	65.80	Granivore (grain and seeds)	1.68	0.0255	0.10	0.0015
	65.80	Frugivore (fruit)	3.36	0.0510	0.20	0.0031
	65.80	Herbivore (short grass)	17.86	0.2714	1.07	0.0163
	65.80	Herbivore (long grass)	10.03	0.1524	0.60	0.0091
	65.80	Herbivore (forage crops)	15.38	0.2338	0.92	0.0140

Table 16 Tier 1 Level Risk of Isofetamid to Aquatic Organisms From Runoff and Spray Drift

Organism	Exposure	PMRA Number	Endpoint	Spray Drift		Runoff		
				EEC (mg a.i./L)	RQ	EEC (mg a.i./L)	RQ	LOC exceeded?
Freshwater species								
Daphnia magna	Chronic 21-day	2273897	NOEC = 0.8 mg a.i./L	0.032	0.04	0.089	0.11	No
Rainbow trout	Acute 96 hr	2273901	LC_{50} = 0.227 mg a.i./L	0.032	0.14	0.097	0.43	No
Bluegill sunfish	Acute 96 hr	2273902	LC_{50} > 0.32 mg a.i./L	0.032	>0.1	>0.097	>0.30	No
Fathead minnow	Chronic – Early Life Stage 5-d embryo and 28-d juvenile	2273905	NOEC = 0.86 mg a.i./L	0.032	0.04	0.089	1.03	Yes
Amphibians	Acute 96 hr	2273901	LC_{50} = 0.227 mg a.i./L (from rainbow trout acute)	0.17	0.75	0.24	1.06	Yes
	Chronic – Early Life Stage	2273905	NOEC = 0.86 mg a.i./L (from fathead	0.032	0.04	0.148	1.72	Yes

Organism	Exposure	PMRA Number	Endpoint	Spray Drift		Runoff		
				EEC (mg a.i./L)	RQ	EEC (mg a.i./L)	RQ	LOC exceeded?
	5-d embryo and 28-d juvenile		minnow trout ELS)					
Marine species								
Mollusk *Crassostrea virginica*	Acute 96 hr	2273900	EC_{50} = 0.22 mg a.i./L	0.032	0.15	0.097	0.44	No
Sheepshead minnow	Acute 96 hr	2273904	LC_{50} > 0.28 mg a.i./L	0.032	>0.11	0.097	>0.35	No
Marine alga *Skeletonema costatum*	Acute 96 hr	2273916	EC_{50} = 0.45 mg a.i./L	0.032	0.07	0.097	0.22	No

Figure 1 Transformation Pathway for Isofetamid in Soil Under Aerobic Conditions



3-MTCA and 3-MTCAM were only tentatively identified

Figure 2 Photolysis Transformation Pathway of Isofetamid in Water

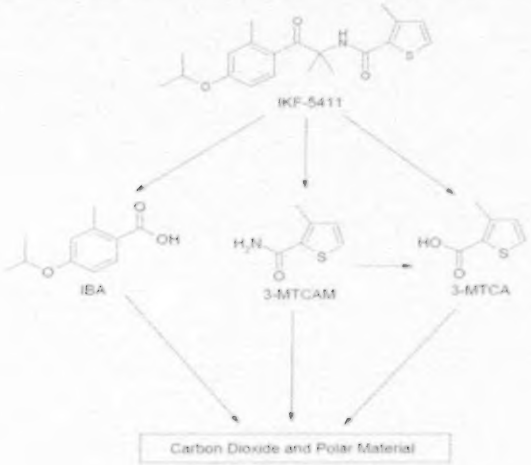


Table 17 Registered Alternatives (as of April 25, 2014)

Crop	Pest	Registered active ingredient (in FRAC Fungicide Group)
Grape	Botrytis bunch rot (*Botrytis cinerea*)	*Aureobasidium pullulans* DSM 14940 and 14941 (NC) *Bacillus subtilis* QST 713 strain (44) Boscalid (7) + pyraclostrobin (11) Cyprodinil (9) Fluopyram (7) Fluopyram (7) + pyrimethanil (9) Iprodione (2) Pyrimethanil (9)
Lettuce (head and leaf)	Sclerotinia drop (*Sclerotinia minor, Sclerotinia sclerotiorum*)	*Bacillus subtilis* QST 713 strain (44) Boscalid (7) *Coniothyrium minitans* CON/M/91-08 (NC) Dicloran (14) Ferbam (M3) Iprodione (2) Penthiopyrad (7)
Rapeseed (Crop Subgroup 20A)	Sclerotinia stem rot (*Sclerotinia sclerotiorum*)	Azoxystrobin (11) *Bacillus subtilis* QST 713 strain (44) Boscalid (7) *Coniothyrium minitans* CON/M/91-08 (NC) Cyprodinil (9) + fludioxonil (12) Fluxapyroxad (7) Fluxapyroxad (7) + pyraclostrobin (11) Iprodione (2) Metconazole (3) Penthiopyrad (7) Picoxystrobin (11) Prothioconazole (3)

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Isofetamid is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for isofetamid in Canada are the same as corresponding tolerances to be promulgated in the United States.

Once established, the American tolerances for isofetamid will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[9] listed for isofetamid in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

[9] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2273821	2013, Part 2 Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient Technical Isofetamid Fungicide, DACO: 2.0,2.1,2.10,2.2,2.3,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9 CBI
2273822	2012, PRODUCT CHEMISTRY STUDIES FOR TECHNICAL ISOFETAMID (IKF-5411) - SERIES 61 - PRODUCT IDENTITY AND COMPOSITION - DESCRIPTION OF MATERIALS USED TO PRODUCE THE PRODUCT - DESCRIPTION OF PRODUCTION PROCESS - DISCUSSION OF FORMATION OF IMPURITIES, DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.13.2 CBI
2273823	2012, PRODUCT CHEMISTRY STUDIES FOR TECHNICAL ISOFETAMID (IKF-5411), DACO: 2.12.1,2.13.1,2.13.3 CBI
2273824	2000, PRODUCT CHEMISTRY STUDIES FOR TECHNICAL ISOFETAMID (IKF-5411) - SERIES 63 -, DACO: 2.13.2,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7, 2.14.8,2.14.9
2346686	2013, NMR, DACO: 2.13.2 CBI
2346687	2013, Interpretation of NMR data, DACO: 2.13.2 CBI
2273730	2013, Part 3 Chemistry for Registration of End-Use Product - Isofetamid 400SC Fungicide - 3.1 Product Identification, DACO: 3.1.1,3.1.2,3.1.3,3.1.4
2273731	2012, PRODUCT CHEMISTRY STUDIES FOR ISOFETAMID 400SC - SERIES 61 - PRODUCT IDENTITY AND COMPOSITION - DESCRIPTION OF MATERIALS USED TO PRODUCE THE PRODUCT - DESCRIPTION OF FORMULATION PROCESS - DISCUSSION OF FORMATION OF IMPURITIES, DACO: 3.2.1,3.2.2,3.2.3 CBI
2273732	2012, PRODUCT CHEMISTRY STUDIES FOR ISOFETAMID 400SC - SERIES 62 -, DACO: 3.3.1,3.4,3.4.1 CBI
2273733	2011, PRODUCT CHEMISTRY STUDIES FOR ISOFETAMID 400SC (IKF-5411) - SERIES 63 -, DACO: 3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9
2327348	2013, IKF-5411 400SC Storage Stability (PET containers), DACO: 3.5.10
2327349	2013, IKF-5411 400SC Storage Stability (HDPE containers), DACO: 3.5.10
2346669	2013, Revised description of formulation process, DACO: 3.2.2 CBI
2346671	2013, Revised physical and chemical characteristics summary for Isofetamid 400SC, DACO: 3.5
2273876	2010, INDEPENDENT LABORATORY VALIDATION OF ISHIHARA SANGYO KAISHA (ISK) RESIDUE ANALYTICAL METHOD FOR THE DETERMINATION OF IKF-5411 AND ITS METABOLITES 4HP IN SOIL, DACO: 8.2.2.1

2273877	2010, VALIDATION OF THE RESIDUE ANALYTICAL METHOD FOR THE DETERMINATION OF IKF-5411 AND ITS METABOLITE 4HP IN SOIL, DACO: 8.2.2.1
2273878	2012, VALIDATION OF AN ANALYTICAL METHOD FOR THE DETERMINATION OF IKF-5411 AND 4HP IN SEDIMENT, DACO: 8.2.2.2
2273879	2012, IKF-5411 AND ITS METABOLITES 3-MTCAM, IBA AND PPA: VALIDATION OF AN ANALYTICAL METHOD FOR THE DETERMINATION OF RESIDUES IN SURFACE AND DRINKING WATER, DACO: 8.2.2.3

2.0 Human and Animal Health

PMRA Document Number	Reference
2273826	2010, IKF-5411 TECHNICAL: ACUTE ORAL TOXICITY TO THE RAT (ACUTE TOXIC CLASS METHOD), DACO: 4.2.1
2273827	2010, IKF-5411 TECHNICAL: ACUTE DERMAL TOXICITY TO THE RAT, DACO: 4.2.2
2273828	2010, IKF-5411 TGAI: ACUTE 4 HOUR (NOSE ONLY) INHALATION STUDY IN THE RAT, DACO: 4.2.3
2273829	2010, IKF-5411 TECHNICAL: EYE IRRITATION STUDY IN RABBITS, DACO: 4.2.4
2273830	2010, IKF-5411 TECHNICAL: SKIN IRRITATION STUDY IN RABBITS, DACO: 4.2.5
2273831	2010, IKF-5411 TECHNICAL: SKIN SENSITISATION STUDY IN MICE, DACO: 4.2.6
2273832	2009, IIKF-5411 TECHNICAL: VALIDATION OF AN ANALYTICAL METHOD IN THE DIET FOR RODENTS, DACO: 4.3.4.4
2273833	2009, IKF-5411 TECHNICAL: STABILITY STUDY IN DIET FOR RODENTS, DACO: 4.3.4.4
2273834	2010, IKF-5411 TECHNICAL: VALIDATION OF AN ANALYTICAL METHOD IN THE 1% SODIUM CARBOXYMETHYL CELLULOSE SOLUTION, DACO: 4.3.4.4
2273835	2010, VALIDATION OF AN ANALYTICAL METHOD AND LIQUID FORMULATION PREPARATION, HOMOGENEITY AND STABILITY, DACO: 4.3.4.4
2273836	2011, IKF-5411 TECHNICAL: REPEATED DOSE 90-DAY ORAL TOXICITY STUDY IN RAT, DACO: 4.3.1
2273837	2011, IKF-5411 TECHNICAL: PRELIMINARY CARCINOGENICITY STUDY BY DIETARY ADMINISTRATION TO CD-I MICE FOR 13 WEEKS, DACO: 4.3.1
2273839	2011, IKF-5411 TECHNICAL: REPEATED DOSE 90-DAY ORAL TOXICITY STUDY IN DOGS, DACO: 4.3.2
2273840	2010, IKF-5411 TECHNICAL: VALIDATION OF AN ANALYTICAL METHOD IN THE DIET FOR DOGS, DACO: 4.3.2
2273842	2003, IKF-5411 TECHNICAL: REPEATED DOSE 1-YEAR ORAL TOXICITY STUDY IN DOGS, DACO: 4.3.2
2273843	2011, IKF-5411 TECHNICAL: REPEATED DOSE 28-DAY ORAL TOXICITY STUDY IN RATS, DACO: 4.3.3
2273844	2010, IKF-5411 TECHNICAL: PILOT TOXICITY STUDY IN DOGS, DACO: 4.3.3
2273845	2011, IKF-5411 TECHNICAL: REPEATED DOSE 28-DAY ORAL TOXICITY STUDY IN DOGS, DACO: 4.3.3
2273846	2011, IKF-5411 TECHNICAL: TOXICITY STUDY BY DERMAL ADMINISTRATION TO RATS FOR 4 WEEKS, DACO: 4.3.5
2273847	2012, IKF-5411 TECHNICAL: REPEATED DOSE 1-YEAR ORAL TOXICITY STUDY IN RATS, DACO: 4.4.1
2273848	2012, IKF-5411 TECHNICAL CARCINOGENICITY STUDY BY DIETARY ADMINISTRATION TO CD-I MICE FOR 78 WEEKS, DACO: 4.4.2
2273850	2012, IKF-5411 TECHNICAL: CARCINOGENICITY STUDY IN RATS, DACO: 4.4.3

2273852	2012, IKF-5411 TECHNICAL: 4 WEEK DIETARY IMMUNOTOXICITY STUDY IN THE FEMALE CD-I MOUSE, DACO: 4.5
2273854	2011, IKF-5411 TECHNICAL: REPRODUCTION TOXICITY STUDY IN RATS PRELIMINARY STUDY, DACO: 4.5.1
2273857	2012, IKF-5411 TECHNICAL: REPRODUCTION TOXICITY STUDY IN RATS (2ND REVISED FINAL REPORT), DACO: 4.5.1
2273859	2012, AN ORAL (GAVAGE) ACUTE NEUROTOXICITY STUDY OF IKF-5411 IN RATS, DACO: 4.5.12
2273861	2011, A 90-DAY DIETARY NEUROTOXICITY STUDY OF IKF-5411 IN RATS, DACO: 4.5.13
2273863	2010, IKF-5411 TECHNICAL: PRELIMINARY EMBRYO-FETAL TOXICITY STUDY BY ORAL (GAVAGE) ADMINISTRATION TO CD RATS, DACO: 4.5.2
2273865	2010, IKF-5411 TECHNICAL: EMBRYO-FETAL TOXICITY STUDY BY ORAL (GAVAGE) ADMINISTRATION TO CD RATS, DACO: 4.5.2
2273866	2010, IKF-5411 TECHNICAL: TERATOGENICITY STUDY IN RABBITS PRELIMINARY STUDY, DACO: 4.5.3
2273867	2012, IKF-5411 TECHNICAL: TERATOGENICITY STUDY IN RABBITS, DACO: 4.5.3
2273868	2002, IKF-5411 TECHNICAL: BACTERIAL REVERSE MUTATION TEST, DACO: 4.5.4
2273869	2011, IKF-5411 TECHNICAL: GENE MUTATION TEST IN MOUSE LYMPHOMA CELLS, DACO: 4.5.5
2273870	2010, IKF-5411 TECHNICAL: CHROMOSOME ABERRATION TEST IN CULTURED MAMMALIAN CELLS, DACO: 4.5.6
2273872	2010, IKF-5411 TECHNICAL: MICRONUCLEUS TEST IN MICE, DACO: 4.5.7
2273873	2011, [14C]IKF-5411: ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION IN THE RAT, DACO: 4.5.9
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2273736	2011, IKF-5411 400SC: ACUTE DERMAL TOXICITY TO THE RAT, DACO: 4.6.2
2273737	2010, IKF-5411 400SC: ACUTE 4 HOUR (NOSE ONLY) INHALATION STUDY IN THE RAT, DACO: 4.6.3
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2273739	2011, IKF-5411 400SC: SKIN IRRITATION STUDY IN RABBITS, DACO: 4.6.5
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2273760	2012, [14C]IKF-5411: METABOLISM IN FRENCH BEAN, DACO: 6.3
2273761	2012, IKF-5411 AND ITS METABOLITE GPTC VALIDATION OF METHODOLOGY FOR THE DETERMINATION OF RESIDUES IN GRAPE, LETTUCE, OILSEED RAPE SEED AND DRY BEAN, DACO: 7.2.1,7.2.2
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2273770	2012, Magnitude of Residues of IKF-5411 on Canola - US A & Canada in 2011, DACO: 7.4.1,7.4.2
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2273773	2012, IKF-5411: [14C-Th]IKF-5411 UPTAKE AND METABOLISM IN CONFINED ROTATIONAL CROPS, DACO: 7.4.3
2273774	2013, Field Accumulation of IKF-5411 in Rotational Crops - USA in 2011, DACO: 7.4.4
2273778	2012, IKF-5411 400 SC (IBE 4022) RESIDUE STUDY (AT HARVEST AND PROCESSING) WITH IKF-5411 400 SC (IBE 4022) APPLIED TO WINE GRAPES IN GERMANY, NORTHERN FRANCE, SOUTHERN FRANCE AND SPAIN IN 2011, DACO: 7.4.5
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3.0 Environment

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2273878 2012, VALIDATION OF AN ANALYTICAL METHOD FOR THE DETERMINATION OF IKF-5411 AND 4HP IN SEDIMENT, DACO: 8.2.2.2

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2273881 2010, [14C]IKF-5411: PHOTODEGRADATION ON SOIL SURFACE, DACO: 8.2.3.3.1

2273882 2012, [14C]IKF-5411: PHOTODEGRADATION AND QUANTUM YIELD IN STERILE, AQUEOUS SOLUTION, DACO: 8.2.3.3.2

2273883 2010, [14C]IKF-5411: AEROBIC SOIL METABOLISM AND DEGRADATION - AMENDED REPORT, DACO: 8.2.3.4.2

2273884 2010, [14C]IKF-5411: THE RATE OF DEGRADATION IN THREE SOILS UNDER AEROBIC CONDITIONS, DACO: 8.2.3.4.2

2273885 2010, [14C]IKF-5411: THE RATE OF DEGRADATION IN ONE SOIL AT 10°C UNDER AEROBIC CONDITIONS, DACO: 8.2.3.4.2

2273886 2010, [14C]IKF-5411: ANAEROBIC SOIL METABOLISM AND DEGRADATION, DACO: 8.2.3.4.4

2273887 2012, [14C]IKF-5411: DEGRADATION IN WATER-SEDIMENT SYSTEMS UNDER AEROBIC CONDITIONS, DACO: 8.2.3.5.4

2273888 2011, [14C]IKF-5411: DEGRADATION IN WATER-SEDIMENT SYSTEMS UNDER ANAEROBIC CONDITIONS, DACO: 8.2.3.5.6

2273889 2010, [14C]IKF-5411: ADSORPTION/DESORPTION IN FIVE SOILS, DACO: 8.2.4.2

2273890 2012, 4HP (METABOLITE OF IKF-5411): ADSORPTION/DESORPTION IN

FIVE SOILS, DACO: 8.2.4.2

2273891 2013, Storage, Disposal and Decontamination Summary: Technical Isofetamid, DACO: 8.4.1

2273779 2013, Summary of the Environmental Fate of IKF-5411(Isofetamid), DACO: 8.1

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2273785 2012, Terrestrial Field Dissipation of IKF-5411 Applied to Bareground in Kerman, CA - USA 2010, DACO: 8.3.2

2273787 2012, Terrestrial Field Dissipation of IKF-5411 Applied to Bareground in Northwood, ND - USA 2010, DACO: 8.3.2

2273788 2013, Terrestrial Field Dissipation of IKF-5411 Applied to Bareground in Aberdeen, SK, Canada - 2010, DACO: 8.3.2

2273789 2013, Field Soil Dissipation for IKF-5411 400SC Applied to Turf in Proctor, AR - USA 2011, DACO: 8.3.2

2273791 2013, Field Soil Dissipation for IKF-5411 400SC Applied to Turf in Goldsboro, NC - USA 2011, DACO: 8.3.2

2273792 2013, Storage, Disposal and Decontamination Summary: Isofetamid 400SC Fungicide, DACO: 8.4.1

2273892 2013, Summary of the Ecotoxicology of IKF-5411(Isofetamid), DACO: 9.1

2273893 2011, IKF-5411 TECHNICAL ACUTE TOXICITY (LC50) TO THE EARTHWORM, DACO: 9.2.3.1

2273895 2010, IKF-5411 TECHNICAL ACUTE TOXICITY TO HONEY BEES, DACO: 9.2.4.1, 9.2.4.2

2273896 2010, A 48-HOUR ACUTE IMMOBILIZATION STUDY OF IKF-5411 TECHNICAL WITH DAPHNIA MAGNA, DACO: 9.3.2

2273897 2011, DAPHNIA MAGNA REPRODUCTION STUDY OF IKF-5411 TECHNICAL, DACO: 9.3.3

2273898 2012, [14C]-IKF-5411: SEDIMENT-WATER CHIRONOMUS RIPARIUS TOXICITY TEST USING SPIKED SEDIMENT, DACO: 9.3.4

2273899 2012, IKF-5411 TECHNICAL: A 96-HOUR FLOW-THROUGH ACUTE TOXICITY TEST WITH THE SALTWATER MYSID, DACO: 9.4.2

2273900 2012, IKF-5411 TECHNICAL: A 96-HOUR SHELL DEPOSITION TEST WITH THE EASTERN OYSTER, DACO: 9.4.4

2273901 2012, IKF-5411 Technical ACUTE TOXICITY TO RAINBOW TROUT, DACO: 9.5.2.1

2273902 2012, IKF-5411 TECHNICAL: A 96-HOUR FLOW-THROUGH ACUTE TOXICITY TEST WITH THE BLUEGILL, DACO: 9.5.2.2

2273903 2010, A 96-HOUR ACUTE TOXICITY STUDY OF IKF-5411 TECHNICAL WITH COMMON CARP, DACO: 9.5.2.3

2273904 2012, IKF-5411 TECHNICAL: A 96-HOUR FLOW-THROUGH ACUTE TOXICITY TEST WITH THE SHEEPSHEAD MINNOW, DACO: 9.5.2.4

2273905 2011, IKF-5411 TECHNICAL: AN EARLY LIFE-STAGE TOXICITY TEST WITH THE FATHEAD MINNOW, DACO: 9.5.3.1

2273906 2011, IKF-5411 TECHNICAL ACUTE ORAL TOXICITY (LD50) TO THE BOBWHITE QUAIL, DACO: 9.6.2.1

2273907 2012, IKF-5411 TECHNICAL: ACUTE ORAL TOXICITY (LD50) TO THE MALLARD DUCK, DACO: 9.6.2.2

2273908 2012, IKF-5411 TECHNICAL: AN ACUTE ORAL TOXICITY STUDY WITH THE CANARY (Serinus canaria), DACO: 9.6.2.3

2273909 2011, IKF-5411 TECHNICAL DIETARY TOXICITY (LC50) TO THE BOBWHITE QUAIL, DACO: 9.6.2.4

2273910 2011, IKF-5411 TECHNICAL DIETARY TOXICITY (LCSO) TO THE MALLARD DUCK, DACO: 9.6.2.5

2273911 2012, IKF-5411 ASSESSMENT TO DETERMINE THE EFFECTS ON REPRODUCTION IN THE BOBWHITE QUAIL, DACO: 9.6.3.1

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2273913 2012, IKF-5411 TECHNICAL: A 96-HOUR TOXICITY TEST WITH THE FRESHWATER ALGA (ANABAENA FLOS-AQUAE), DACO: 9.8.2

2273914 2012, IKF-5411 TECHNICAL: A 96-HOUR TOXICITY TEST WITH THE FRESHWATER ALGA (PSEUDOKIRCHNERIELLA SUBCAPITATA), DACO: 9.8.2

2273915 2012, IKF-5411 TECHNICAL: A 96-HOUR TOXICITY TEST WITH THE

FRESHWATER DIATOM (Navicula pelliculosa), DACO: 9.8.2

2273916 2012, IKF-5411 TECHNICAL: A 96-HOUR TOXICITY TEST WITH THE MARINE DIATOM (Skeletonema costatum), DACO: 9.8.3

2273917 2012, IKF-5411 TECHNICAL: A 7-DAY STATIC-RENEWAL TOXICITY TEST WITH DUCKWEED (Lemna gibba G3), DACO: 9.8.5

2273918 2012, IKF-5411 400SC Terrestrial (Non-target) Plant Growth Test Seedling Emergence, DACO: 9.8.6

2273919 2012, IKF-5411 400SC Terrestrial (Non-target) Plant Growth Test Vegetative Vigour, DACO: 9.8.6

2273793 2013, Summary of the Ecotoxicology of IKF-5411(Isofetamid), DACO: 9.1

2273795 2012, IKF-5411 400SC ACUTE TOXICITY TO HONEY BEES, DACO: 9.2.4.1, 9.2.4.2

2273796 2010, IKF-5411 400 SC ACUTE TOXICITY TO TYPHLODROMUS PYRI IN THE LABORATORY, DACO: 9.2.8

2273797 2010, IKF-5411 400SC ACUTE TOXICITY TO APHIDIUS RHOPALOSIPHI IN THE LABORATORY, DACO: 9.2.8

2273798 2011, A 48-HOUR ACUTE IMMOBILIZATION STUDY OF IKF-5411 400SC IN DAPHNIA MAGNA, DACO: 9.3.2

2273799 2011, A 96-HOUR ACUTE TOXICITY STUDY OF IKF-5411 400SC IN COMMON CARP, DACO: 9.5.2.3

4.0 Value

2273678 2013, Value Summary for Isofetamid 400SC Agricultural Fungicide for Control of Diseases of Grape, Lettuce (Head and Leaf), Rapeseed Crop Group 20A, Low Growing Berry Crop Group 13-07G and Turf, DACO: 10.1,10.2.1,10.2.2,10.2.3.1, 10.2.3.3,10.3,10.4,10.5

2273680 2013, Canola - Sclerotinia, DACO: 10.2.3.3

2273681 2013, Canola - Sclerotinia, DACO: 10.2.3.3

2273682 2013, Grape - Botrytis bunch rot, DACO: 10.2.3.3

2273684 2013, Strawberry - Grey mold, DACO: 10.2.3.3

2273685 2013, Strawberry - Botrytis, DACO: 10.2.3.3

2273686 2013, Lettuce - sclerotinia drop, DACO: 10.2.3.3

2273687 2013, Lettuce - sclerotinia drop, DACO: 10.2.3.3

2273688 2013, Turf - Dollar spot, DACO: 10.2.3.3

2273689 2013, Canola - sclerotinia, DACO: 10.2.3.3

2273690 I. S. Bay, R. W. Doody, T. N. Nguyen, R. A. Choudhury, D. Gubler, 2013, Grape – Botrytis bunch rot, DACO: 10.2.3.3

2273695 N. O. Halbrendt, H. K. Ngugi, M. Grove, 2013, Grape - Botrytis bunch rot, DACO: 10.2.3.3

2273697 2013, Grape - Botrytis bunch rot, DACO: 10.2.3.3

2273699 2013, Grape - Botrytis bunch rot, DACO: 10.2.3.3

2273700 2013, Strawberry - foliar and post-harvest disease, DACO: 10.2.3.3

2273704 2013, Strawberry - gray mold, DACO: 10.2.3.3

2273707 2013, Lettuce - sclerotinia leaf drop, DACO: 10.2.3.3

2273708 P. Koch, S. Soper, B. V. Ryzin, J. Soper, J. Kerns, 2013, Turf - Dollar spot, DACO: 10.2.3.3

2273709 2013, Turf - Dollar spot, DACO: 10.2.3.3

2273710 W.Uddin, B. Aynardi, 2013, Turf - Dollar spot, DACO: 10.2.3.3

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2273713 2013, Turf - Dollar spot, DACO: 10.2.3.3

2273714 2013, Turf - Dollar spot, DACO: 10.2.3.3

2273715 2013, Canola - sclerotinia, DACO: 10.2.3.3

2273717 2013, Canola - sclerotinia, DACO: 10.2.3.3

2273719 2013, Canola - sclerotinia, DACO: 10.2.3.3

2273720 2013, Strawberry - gray mold, DACO: 10.2.3.3

2273721 2013, Lettuce - sclerotinia leaf drop, DACO: 10.2.3.3

2273723 2013, Iceberg Lettuce - sclerotinia minor, DACO: 10.2.3.3

2273725 J.M. Vargas, N. Dykema, R. Detweiler, M. Pressler, 2013, Turf - Dollar spot, DACO: 10.2.3.3

2273726 J. Popko, K. Campbell-Nelson, G. Jung, 2013, Turf - Dollar spot, DACO: 10.2.3.3

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B. Additional Information Considered

i) Published Information

1.0 Environment

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